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Brain

A Journal of Neürology

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VOLUME LIX

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EDITOR.

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BRAIN.

PART 1, VOL. 59.

THE NEWER KNOWLEDGE OF VIRUS DISEASES OF THE NERVOUS SYSTEM: A REVIEW AND AN INTERPRETATION.

BY E. WESTON HURST.

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RECENT years have seen a considerable extension of our knowledge in the field of neurotropic viruses. The advance might have been greater but for the fact that much of the work done has been one-sided, usually by workers with little special knowledge of the nervous system [24], less often by neuro-histologists who have dealt with the end results of virus activity in the nervous system and have neglected entirely the experimental investigations which alone could answer many of the questions they have asked concerning pathogenesis. A review taking into account both the viruses and the terrain on which they manifest their activity will be of service in showing not only what has been accomplished in this sphere, but also the numerous gaps to be filled before we can begin to do more than guess at the fundamental processes involved.

DEFINITIONS.

At the outset it is essential that an exact meaning should be attached to certain terms qualifying the viruses under discussion. There is to-day much evidence to support, and but little to contradict, the belief that viruses are obligatory intracellular parasites [23]; also it cannot be doubted that among themselves viruses differ greatly in their cellular affinities. We may, therefore, reasonably hope that more complete knowledge will lead to a classification, based on the precise cellular tropisms of its members, of a group of contagia at present recognized only by the expression of their pathogenic tendencies.

Any but the most superficial analysis shows that many of the peculiarities of behaviour which might be taken as criteria of neurotropism in a particular virus are not exhibited by all viruses which may fairly be designated neurotropic. This difficulty in establishing criteria does not, however, justify the indiscriminate use of the adjective, with which, apparently, many writers qualify any virus capable of evoking an intradural lesion, whether that lesion affects primarily the nervous elements or not. Such confusion of thought is implicit in the nomenclature even of so distinguished a contributor as Levaditi. For example, this author uses the term "ectodermoses neurotropes" [16, 17, &c.] to cover a group of diseases including rabies, poliomyelitis, herpes and vaccinia. Apart from some recent unconfirmed observations [171], it has never been shown that the first two viruses have any affinity for the surface ectoderm; the herpes virus attacks and produces specific lesions in cells derived from all three embryonic layers; while, as Levaditi himself showed, cerebral vaccinia is primarily a process in the mesoderm of the nervous system, and elsewhere in the body this virus evokes mesodermal lesions. Levaditi's more recent "mesodermose neurotrope" [98] in relation to the virus of lymphogranuloma inguinale has even less precise significance; on the one hand the virus is not neurotropic in the commonly accepted sense of invading the central nervous system from a focus of peripheral inoculation, on the other it manifests no special affinity for the mesoderm of the brain as opposed to the mesoderm of the body generally. It is but one step further to class the tubercle bacillus as a neurotropic organism because on occasion it is the cause of tuberculous meningitis. The present writer can find only one characteristic common to all viruses which can legitimately be termed neurotropic—namely, that they all attack, primarily and directly, the nerve cell.

In this paper, then, "neurotropic virus" will be held to signify a virus capable of primary and direct attack on the specific nervous elements—nerve cells, and, in many cases, glial cells. Some such viruses have no apparent affinity for other cells and tissues; these are the "stricter neurotropes." Many viruses, however, while demonstrably neurotropic also possess obvious affinities for non-nervous tissues; these will be designated "pantropic" [139]. Finally, in the case of viruses exhibiting no apparent tendency to invade the central nervous system from a focus of peripheral infection, and which, when inoculated directly into the brain, create lesions by virtue of a primary action on the mesoderm, the perhaps less satisfactory term "viscerotropic" will be employed. When using these terms it is necessary in some cases to state clearly the animal species on which observations have been carried out, since a virus may behave quite differently in different hosts. Thus the virus of herpes febrilis produces in man a superficial vesicular lesion, while in the rabbit many strains invade the nervous system to set up encephalitis [61]. The pseudorabies virus again is pantropic in the rabbit [139], but apparently strictly neurotropic in the rhesus monkey [140].

HISTOLOGICAL FEATURES OF VIRUS DISEASES.

Lesions in the Nervous System due to Neurotropic Viruses.

In all probability viruses are obligatory intracellular parasites [23]. If, therefore, the adjective neurotropic as applied to certain viruses has any significance, we should logically expect such viruses to be capable of a primary and direct attack on the nerve cells. Such is in fact the case. Yet the older literature on so typical a neurotropic virus disease as poliomyelitis ascribed the lesions in nerve cells wholly or in large part to impaired nutrition, resulting from interstitial inflammation, &c.; almost alone among the older authors Rissler [130] recognized the true sequence of events, recently emphasized by many [101, 103, 104, 113, 114, 121, 122, 128, 133].

The truth of this matter cannot be ascertained by studying human post-mortem material in which tissue and vascular reaction have had time to appear and dominate the histological picture: only examination in the earliest phases of the disease, as is possible in the experimental animal, can determine the structures first affected and the relative importance of the various changes seen later. A further point needing mention is that of technique. The German influence in neuropathology has rightly made the Nissl method the standard staining process for the nervous system. But in the study of lesions caused by viruses the technique suffers from serious defects. It is incapable of revealing clearly the cytological alterations most characteristic of such infections, and the preliminary fixation required by the method is not well adapted to their demonstration. Again, in the last stages of nervous degeneration the necrotic neurons are displayed far more effectively by other means. In fact, the use of some such fixative as Zenker with acetic acid, or sublimate-formol, and staining with phloxin- or eosin-methylene blue, Giemsa or even hæmatoxylin and eosin, are far more useful for proper evaluation of the histological picture of virus diseases of the nervous system than is the Nissl method.

The microscopical appearances of nerve cells affected by a virus vary with the acuteness or otherwise of the disease process. In hyperacute and acute conditions, and hence commonly in experimental infections with viruses of exalted virulence, though also not infrequently in some naturally occurring infections, the type lesion is acute necrosis of the neurons. The cytoplasm is shrunken and strongly eosinophilic, the nucleus pyknotic, karyorrhectic, fading or absent; in the brief pre-necrotic phase various types of neuronal change described by Nissl may be seen, but especially the so-called ischæmic cell-change and the "severe cell-change." The more virulent strains of poliomyelitis virus acting on the monkey's cord destroy many of the cells of the anterior horns in this abrupt manner, and if the animal is sacrificed at just the right moment the histological picture may be almost uncomplicated by the rapidly following cellular exudation [114]. Similar necrosis may be met in one situation or another in experimental rabies [148, 163, 169], louping-ill [79, 80, 85], herpetic encephalitis [59, 69], equine encephalomyelitis [55], yellow fever [217, 218], pseudorabies [138], virus III infection [212], &c., either from catastrophic destruction within but a few hours, or from rather less acute degeneration often accompanied in the earlier stages by the formation of specific inclusions. In extremely acute infections, e.g. pseudorabies in the rabbit [138], the animal may die before further developments have time to occur, and the picture is then unequivocally that of primary and direct attack on the nerve cells. Usually, however, the animal survives longer, and then, as in all lesions accompanied by necrosis of tissue, polymorphonuclear leucocytes migrate swiftly into the damaged areas to attack and lyse the dead cells. These leucocytes, which may even penetrate the vacuoles of an incompletely necrotic neuron, themselves soon manifest karyorrhexis and other degenerative phenomena, and if death is still further delayed they are engulfed together with persisting remnants of the ganglion cells by microglial phagocytes; oxydase granules may persist in the nervous tissues longer than do recognizable leucocytes [114]. Many descriptions of these later changes have been contributed to the literature by writers who have failed to detect or correctly evaluate the essential primary pathological process in the neurons.

Side by side with this extremely acute destruction, slower forms of degeneration of nerve cells may obtain; in many diseases, e.g. poliomyelitis and rabies in man, they are the principal or only feature. It is in neurons so affected that, in the diseases in which they occur, cellular inclusions are most fruitfully sought. These inclusions may be sufficiently distinctive to be of diagnostic value, but their present interest lies in the support they afford to the theory of intracellular parasitism of the virus. Nerve cells succumbing to the slower forms of degeneration are phagocyted by the microglia without leucocytic intervention, though cells of the lymphocytic series may make their appearance in the tissues. Diffuse and focal microglial proliferation thus comes to be a prominent finding in many virus diseases; the Babes nodules [149], supposed to be characteristic of rabies, and Wickman's polyblasts in poliomyelitis [135] are of this origin. Generally speaking, tissue infiltration is more marked in the less acute conditions—in this respect human may be contrasted with monkey poliomyelitis. In slowly progressive maladies (e.g. Borna disease) it is more difficult to demonstrate the primary attack on the nerve cells except in so far as these exhibit specific cytological alterations, presumably because the sensitive mesoderm reacts to the earliest changes in the nerve cells while there is still little alteration of the normal microscopical picture.

Finally, in every virus disease a proportion, often considerable, of ganglion cells remains apparently unaffected. It is rather exceptional to find inclusions in otherwise normal cells, though this does occur in the cornu Ammonis in rabies [186], and in Borna disease [41]. Nicolau, Nicolau and Galloway's contention that the presence of the inclusion represents the successful termination of the struggle between virus and cell is certainly not of general application, for in pseudorabies [138], infection with B. virus [37], yellow fever [221], &c., the earliest change in still normal cells which will later undergo necrosis is the development of acidophilic nuclear inclusions; and this process is not to be sharply separated, as Nicolau, Kopciowska and Mathis maintain [221], from the ultimate necrosis of the cell.

In some infections (e.g. pseudorabies, herpes, and infections with B. virus and virus III) the true glia demonstrably shares in the degeneration, and shows inclusions similar to those in the nerve cells; in other diseases, e.g. poliomyelitis and rabies, changes in the glia may well be wholly secondary and reactive. Where over considerable areas the glia accompanies the neurons to complete destruction, subsequent softening and porencephaly may result [18, 60, 140]; with less severe damage a glial-mesodermal scar is the outcome [74, 140], while still less profound injury leads to a pure glial sclerosis [117, 134, 135]. In subacute conditions, such as Borna disease, quite definite activity on the part of the glia may be evident at death.

While, therefore, degeneration in nerve cells and perhaps in glial cells is clearly primary, and at an early stage and in some localities of the nervous system may occur in the absence of any trace of inflammation in the mesodermal structures, this latter phenomenon is an integral part of the later histological picture of most diseases due to neurotropic viruses. Perivascular cuffing often tends to be more marked around the third and fourth ventricles and the iter of Sylvius than elsewhere, even though maximal involvement of nerve cells is encountered in other regions. There is, however, considerable individual variation in the site of maximal reaction, as, for instance, the literature on rabies [152, 166, 168, 172, 175, 176, 181, 182, 184, 185, 187, 190] exemplifies. Like tissue infiltration, perivascular and meningeal exudations are more intense in subacute than in acute infections, but it is seldom doubtful how far they represent a secondary reaction to damage to the ectodermal tissues, and how far a direct and coincident action of the virus on the mesoderm. Thus, observation at successive stages of the various infections renders it certain that in many instances meningeal infiltration represents merely an overflow of inflammatory cells from the overcharged perivascular spaces of the nervous substance [105, 114], though belief in a primary meningitis in poliomyelitis delayed for many years a true conception of the disease. On the other hand, in some diseases meningitis is certainly due to direct action of the virus; thus in pseudorabies in the rabbit [138], B. virus disease [37] and virus III infection [212] the presence of nuclear inclusions in, or even acute necrosis of, meningeal and vascular elements proclaims the specific nature of the lesion. In the latter event polymorphonuclear leucocytes abound in the cellular exudate, though ordinarily, even with many leucocytes in the tissues, mononuclears predominate, and in subacute conditions are the only cells present. After the first few days the mesodermal reaction is the striking histological feature, and it may still be conspicuous months after the initial injury [60, 134, 140].

Perivascular hæmorrhages are frequently described as part of the histological picture of acute poliomyelitis, &c., and there can be no doubt that they are sometimes present. But caution is necessary in interpreting this finding. Small hæmorrhages are readily produced by rough handling during removal of a normal nervous system, and with greatly congested vessels in an acutely inflamed organ it is probably impossible to guarantee their absence. Boemke [5] has recently adopted this attitude in relation to the lesions described as characteristic of electrical shock. It is surely significant that scarcely ever, if indeed ever, are signs of reaction to the effused blood detectable [114]; in view of the work of Carmichael [6] and others such hæmorrhages can have preceded death by at most only a short time.

So far there is no sure evidence that any of the primarily demyelinating diseases are due directly to the action of a filtrable virus.

Lesions in other Viscera due to the Foregoing Viruses.

According to their action on organs other than the nervous system, the neurotropic viruses fall into three groups. Except when they are of the nature of a general response to infection, the lesions evoked in the general viscera by members of the first group (stricter neurotropic viruses, such as the viruses of rabies, Borna disease, &c.) occur primarily in connection with the nervous apparatus of the organ. Thus the infectivity of the buccal secretions in rabies has been associated with the presence of Negri bodies in nerve cells immediately underlying the mucosa, coupled with minute abrasions of the epithelium [173]. In Borna disease characteristic nuclear inclusions are found in the visceral nerve cells in many situations [22]. As examples of the second group the pseudorabies, B., and herpes viruses and virus III may be cited. These are pantropic, and, in addition to producing lesions in nervous tissue, they can under suitable conditions excite specific lesions, usually focal necroses, in many tissues and organs by direct parasitism of their constituent cells and independently of their nervous mechanism [37, 38, 64, 66, 75, 138, 139, 211, 213]. It is with viruses of this second group that specific lesions, such as inclusions and necrosis, are often found in the mesodermal tissues of the pia-arachnoid, &c. With a third group, including equine encephalomyelitis, neurotropic yellow fever and louping-ill viruses, the lesions in the nervous system are very like those caused by members of the first group, and encephalitis is the dominant clinical feature of the infection; these viruses do, however, grow in and exercise their pathogenic action on extraneural tissues, particularly on vascular and epithelial structures, and in this sense are pantropic [56]. As will be seen later, experimental study throws more light on their peculiarities than does histological investigation.

Other Viruses Capable of Evoking Intracranial Lesions.

The foregoing sketch outlines in very general terms the sequence of events in the nervous system infected with the more fully studied neurotropic viruses. Except for virus III, the organisms mentioned are those which under natural circumstances or after inoculation into non-nervous tissue may excite encephalomyelitis; experimental investigation usually reveals their ability to invade and parasitize the central nervous system from a focus of peripheral inoculation. The present-day tendency to inject each and every virus intracerebrally has brought to light the capacity of several, which under natural conditions are the causative agents of diseases in which encephalitis constitutes no part of the clinical or pathological picture, for evoking severe and often fatal inflammation when introduced directly into the brain. The resultant lesions differ fundamentally, however, from those described above, and in the writer's opinion it is not justifiable to classify the organisms responsible, as do some workers, with the neurotropic viruses.

Vaccinia is an example of this kind. During or after the systemic reaction to vaccination, especially with "generalizing" strains, virus may sometimes be detected in the cerebrospinal fluid [202] or nervous tissue [204, 206]; it may persist here in the absence of lesions for as long as forty-one days [201]. Its localization in the brain is facilitated by trauma [204]. Injected extracranially, even into a nerve [201], the virus probably never causes a primary encephalitis, though sometimes the lesion mentioned below may accompany very severe generalized vaccinia [204 and personal observation]. Neurovaccine does not differ materially from testicular or dermal vaccine in its affinity for the brain [209]. Following direct intracerebral or intracisternal inoculation the pathological changes are primarily meningeal, and alterations in the underlying cortex are similar to those accompanying any severe meningitis [203, 205, 207, 208].

The descriptions of the lesions evoked by intracerebral inoculation of the salivary gland virus of guinea-pigs leave little doubt that here again there is a primarily mesodermal reaction (194-195·5). Andrewes [193], it is true, found minor lesions in the nerve cells of the lumbar cord, while in a single guinea-pig he observed intranuclear inclusions in a few nerve cells of the brain; later in his paper, however, he suggests that in this disease the inclusions in the meninges, and presumably those in the brain, may in all probability be regarded as denoting not multiplication of virus, but merely reaction to its presence, and hence have a significance different from that of the inclusions produced by virus III.

Thirdly, most writers agree that after direct intracerebral injection of the virus of lymphogranuloma inguinale an almost pure mesodermal lesion develops [94-96, 98]; the demyelinating condition described by Jonesco-Mihaiesti *et al.* [97] probably resulted from spontaneous disease in the experimental animals [93, 99]. Inoculated by other routes the virus appears to have no affinity for the undamaged [95] or even the damaged [98] nervous system.

In brief, none of these viruses shows particular affinity for nervous tissue; after intracerebral inoculation they merely excite lesions in the mesodermal structures covering and penetrating the brain, as they do under other circumstances in mesodermal and other tissues elsewhere in the body. To classify them as neurotropic is to rob the adjective of any precise meaning, and they are here referred to as viscerotropic viruses.

The Nervous Lesions Due to Some Viruses Less Fully Studied.

In the case of certain other viruses affecting the nervous system our knowledge is still too incomplete to permit of categorical statement, which must be based on adequate experimental as well as histological study.

In dog distemper the nervous system is frequently if not invariably involved together with the general viscera. Not only do the older accounts of the histological findings stress the later reactive phenomena, but in the past infections not due to the virus have been mistaken for distemper. Dunkin and Laidlaw's account of the lesions in the ferret and dog [46] suggest a direct attack by the virus on the nerve cells, as do some of Cerletti's findings [45]. Inclusion bodies of several types have been described in the neurons [44, 47, 48, 50, 169, 192]. The relation of the demyelinating lesion of Perdrau and Pugh [49], or the mixed lesion of Marinesco *et al.* [48] to distemper awaits elucidation.

In the rather similar, though ætiologically distinct, epizootic fox encephalitis [51-53], an apparently direct attack on the ectodermal tissues of the nervous system is overshadowed by vascular lesions in the brain and elsewhere. The presence under certain circumstances of intranuclear inclusions in ependymal cells betokens a degree of ectodermal parasitism of the virus, though the chief feature of the disease is the widespread affliction of vascular endothelium and cells of the reticulo-endothelial system. In a personal communication Dr. R. G. Green informs me that the demyelinating lesion described by Levaditi *et al.* [54], is certainly not typical of the disease, occurring in his experience in only a single animal; it may possibly bear a similar relation to fox encephalitis as does the Perdrau and Pugh lesion to dog distemper, or alternatively may represent another disease entity.

The virus responsible for the St. Louis outbreak of encephalitis [196-200] apparently behaves as a typical neurotropic virus causing necrosis of the nerve cells and other lesions already considered. On the other hand, the virus of lymphocytic choriomeningitis [88-92] appears unusual in that it is the first known virus commonly giving rise under conditions of natural infection to a purely mesodermal lesion in the nervous system.

In the absence of precise knowledge of its experimental behaviour, the exact position of the hog-cholera virus also is hard to define. The nervous lesions of this malady [77, 78] differ from those typical of neurotropic virus diseases in being more or less evenly scattered over grey and white matter, and in a very considerable vascular involvement equally or more marked in organs other than the brain. It is tempting to regard this process as a systemic one affecting the nervous system largely by virtue of its nutritive apparatus.

Conclusions.

On histological grounds we may therefore consider the better-known viruses attacking the nervous system as belonging to two classes, according to whether they strike primarily at the specific neural elements, or exercise their pathogenic action mainly on the mesoderm. The former can be subdivided by their capacity or incapacity for parasitizing non-nervous elements within the nervous axis or elsewhere. If these distinctions are significant, we might anticipate that they would lead to differences in the mode of spread of members of the respective groups, and it is here that the available experimental evidence, fragmentary though it may seem a few years hence, is of value.

EXPERIMENTAL DATA ON THE ROUTES OF INFECTION OF THE NERVOUS SYSTEM.

Spread by the Nerves.

Peripheral nerves of any size consist of medullated and non-medullated nerve-fibres bound together by fibrous tissue. The larger trunks are nourished by special vascular branches, and contain lymphatic channels concerning the central relations of which our knowledge is singularly unprecise. The trend of modern opinion is to believe that centrally these perineural lymphatics do not connect with the subarachnoid space [*see* Abel *et al.*, 1, 2]; such observations as those of Horster and Whitman [12], in which material inoculated intraneurally arrived at once at the nervous axis, in all probability merely indicate that sufficient pressure during injection can rupture the existing barriers, demonstrated histologically by Elman [10]. Some indirect evidence supporting this view will be mentioned presently. The medullary sheaths are interrupted at the nodes of Ranvier, and it seems inconceivable that the relatively inert myelin can provide a medium for rapid transport to the central nervous system; the neurolemmal sheath is highly tenuous except in the vicinity of the nuclei of the cells of Schwann. The axis cylinder, a direct protoplasmic continuation of the body of the neuron, seems to be the chief uninterrupted link between centre and periphery. De Renyi's micro-dissection studies [9] indicate apparently that it, like the rest of the cytoplasm of the nerve cell, is of a very definite consistency, retaining its shape completely when cut into fragments. It is intimately connected with the medullary sheath, leaving no natural peri-axial space; the myelin and neurolemma are less closely joined.

Thiele and Embleton [29] believed that the more soluble substances at least may pass directly up the axis cylinders to the cord. Yuien [35], on the other hand, found that solutions injected into a nerve were conveyed by the perineural spaces to the junction of the anterior and posterior roots, thence by the anterior root to the pia and subpial spaces of the cord, and also along, though not apparently within, the motor root fibres as far as their cells of origin. If sufficient time were allowed the solution passed outwards along the posterior roots, but not along the contralateral anterior root. This and other experiments showed that in the motor nerve the direction of lymph flow is centripetal, in the sensory nerve centrifugal. It should be remarked that in the animal killed one and a half hours after inoculation the solution had already reached the cord, an observation recalling the experience of Horster and Whitman (*loc. cit.*); there is no evidence that viruses travel at this speed.

Sullivan and Mortensen [28·5] injected 0·05 c.c. brominol coloured with scharlach R into the sciatic nerves of rabbits and cats, and by radiography traced its subsequent passage towards the cord; they claimed that after four to six hours gross dissection revealed the coloured oil in the subarachnoid space. The rate of spread was not appreciably diminished when muscular movement was prevented by administering hypnotics.

Using the same solutions as Yuien, Hurst (unpublished experiments), injected the median nerves of monkeys at the level of the bend of the elbow. One, two and a half, four and a half, and seven hours later, no macroscopic or microscopic deposit of Prussian blue could be detected above the cords of the brachial plexus. As time elapsed the reaction at the site of inoculation became progressively weaker, until after twenty-four hours no Prussian blue was precipitated even here. Microscopically, at the level of injection the blue precipitate lay mainly under the connective-tissue sheaths of the nerve bundles and, to a less extent, around small vessels deeper in the bundles; the axis cylinders were coloured diffusely a pale blue for a short distance on either side of the nodes of Ranvier, which are recognized as regions of comparatively great permeability.

In a personal communication Dr. D. Denny-Brown states that though injection of a peripheral nerve of cat or monkey with indian ink or carmine-gelatine most often produces merely a local distension of the connective tissue, occasionally the injection will run some centimetres under the perineurium without pressure. When this occurs from an injection fairly near the cord the inoculum may run under the sheath of the spinal ganglia and pass into the subarachnoid space. The exact pathway of this communication is under investigation, but no evidence has been obtained to show any natural circulation by this route.

The anatomical relations of the olfactory nerve differ from those outlined above. The terminal fibrils are freely exposed on the surface of the olfactory mucosa. The lymphatic channels accompanying the nerve filaments, distinct from the general lymphatic system of the nasal mucosa, connect directly with the subarachnoid space [3; 7, 34], and it has been shown that they furnish ready access to the meninges in the case of bacterial invasion [30, 31].

Experimental evidence of the importance of the nervous pathway in the transmission of rabies [151, 153, 154, 161, 183-185] dates back for many years. Rabies did not develop after intrasciatic inoculation if at the same time the nerve were sectioned and cauterized on the central side; if an inoculated tail were removed within twelve hours of the deposition of virus no disease resulted; section of the nerve supply of a salivary gland prevented infection of the secretion; virus and lesions appeared first in that part of the cord most nearly connected with the site of inoculation. In the case of poliomyelitis similar evidence was available [125, 131, 136]. Centripetal neural spread has since been demonstrated in other virus diseases [36, 63, 67, 69, 70, 72, 139], while Nicolau, Nicolau and Galloway have emphasized the centrifugal march of viruses injected intracerebrally; a remarkable example of the latter phenomenon is furnished by Borna disease, in which the long incubation presumably enables the virus to penetrate to, and produce specific changes in, the most remote ganglia of the peripheral nervous system [22, 43]. Evidence of such spread may, however, be obtained even in some hyperacute conditions [139]. In rabies the possibility of this occurring through the medium of the blood has been eliminated [178, 179]. To the transmission of viruses along pre-formed paths Marinesco has applied the term odogenesis.

Until recently less attention has been paid to the precise transmitting mechanism in the nerves; usually it has been assumed or implied that the perineural lymphatics convey the virus to the cerebrospinal fluid, which then acts as the agent of dissemination to various parts of the nervous system [26]. As has been pointed out, it is by no means certain that such a course is anatomically possible except in the case of the olfactory nerve. Moreover, in poliomyelitis it is exceptional under experimental conditions to recover virus from the fluid [109, 115], at any rate during the incubation period, and in the human disease no such finding is on record [100, 102, 112, 123, 127, 131] [1]; we have seen also that meningitis is not the primary lesion of the disease as was once supposed. In rabies negative results have usually been reported [157, 165, 180]; positive results have sometimes been obtained during the period of nervous symptoms [156, 162, 167]. Herpes virus is not easily found in the fluid in rabbits [63]; it has been detected in human fluid [62] in a case where it was certainly not responsible for the nervous condition present. In any case, recovery of a virus from the fluid when the disease process in the nervous tissue is at its height does not necessarily indicate the path travelled during the incubation period.

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[1] In view of the difficulty of establishing human poliomyelitis virus in the monkey, too much weight should not be attached to the negative results with human cerebrospinal fluid and blood. For the monkey, and in the case of rabies virus, the above argument holds good.

Following previous unsuccessful attempts to detect virus in the fluid during the incubation period of experimental poliomyelitis, Hurst (unpublished experiments) practised intrasciatic inoculation in a monkey; each day during the pre-symptomatic period as much fluid as could be removed with safety (about 3 c.c.) was used to replace that of a fresh animal, which thus received in all perhaps 12 c.c. fluid. Nevertheless it did not develop the disease. Repetition of the experiment again led to a negative result. It is very difficult to believe that in these instances the fluid played any part in the transportation of the virus.

It must, of course, be admitted that experimental infection of the fluid readily produces disease. In experimental poliomyelitis it seems that intracisternal inoculation is followed by penetration of the ependymal surfaces by the virus, after which the course of events is similar to that following intracerebral inoculation [116]. In rabies Speransky found that inoculation into a walled-off area bounded only by meninges led to disease only after great delay; he concluded that the cerebrospinal fluid greatly assists in disseminating the virus [191]. No doubt it does when virus is introduced directly into the fluid, but neither of the observations cited show that this occurs under normal conditions.

On the other hand, there is a growing mass of evidence that the nerve fibres themselves may provide the path to the central nervous system. Although Duboué as far back as 1879 suggested the axis-cylinders as a pathway of infection in rabies [155], and in the case of other diseases the supposition has been again advanced by later writers, notably Levaditi, Goodpasture's observations [65, 67] were the first which can be regarded as affording reasonably clear evidence of this occurrence. After inoculation of herpes virus into an area supplied by the sensory division of the 5th cranial nerve, lesions appeared at a point immediately central to the plane where the sheath of Schwann disappears; in these fibres the myelin sheath is not sufficiently developed to prevent escape of virus into susceptible tissues. In the motor division of the nerve, however, conditions are different, inasmuch as the myelin sheaths are much more substantial; after inoculation into the masseter muscle, the first intracerebral lesions are in the motor ganglion cells of the 5th nerve nucleus, and the heavily medullated fibres pass through a wide zone of susceptible tissue without evidence of neuroglial infection. In the case of rabies less conclusive evidence of axonal spread was forthcoming [160]. However, Marinesco and

Draganesco [20] reported that inoculation of herpetic material below a strongly compressed segment of the sciatic nerve, in which the axons had been completely interrupted, might lead to the disease, and concluded that transmission must have taken place by the perineural lymphatics. Even if these channels do connect with the spinal theca the two views are not necessarily in conflict; in the nerve infection may travel by both routes, but more quickly and favourably by the axis-cylinders. Indications in pseudorabies that the virus causing interstitial lesions in the nerve is not responsible for those in the spinal ganglia, which appear before the ascending neuritis has mounted to the juxta-medullary part of the peripheral nerve [138], support this view; similar histological observations are on record in herpes [72] and in B. virus disease [37]. In B. virus disease the meninges are susceptible to direct attack of the virus, which after intracerebral inoculation evokes specific lesions here, but when myelitis ensues after peripheral inoculation specific changes are seen usually only inside the cord, and not in the meninges through which the infective agent must have passed; this observation again suggests an insulating structure between the susceptible meningeal tissues and the virus, which must in other words be inside the medullary sheaths of the nerve fibres. Returning to Marinesco and Draganesco's results, the fact that the herpes virus is not a strict neurotrope and may infect other tissues, as poliomyelitis and rabies apparently cannot do, may conceivably have an important bearing in allowing it to go through a natural barrier between the perineural lymphatics and the subarachnoid space. A further possibility, that the results were due to the mechanism operative in pseudorabies after inoculation into a denervated area, will be considered later.

In a number of diseases caused by neurotropic viruses it has been remarked that a certain amount of trauma exposing the axis cylinders is necessary to ensure successful intraneural inoculation [71, 115. 159].

In poliomyelitis, Fairbrother and Hurst's study of the march of virus and of lesions during the incubation period, suggested very strongly that this virus also may spread by the axons [109, 115]. Without entering into details, one series of observations may be mentioned which is difficult to explain on any other supposition. After inoculation into the left sciatic nerve the virus first appeared in the lumbar cord, and soon afterwards in the leg area of the right motor cortex. At this time the cervical cord, the arm area of the right motor cortex and the left motor cortex were free from virus. Later, virus appeared in the cervical cord, the leg area of the left motor cortex and in the arm area of the motor cortex of both sides. This behaviour would be expected were the pyramidal fibres the transmitting structures. Similar conclusions have been reached by Faber and Gebhardt in a very detailed study of the disease following nasal instillation [108]. Brodie and Elvidge [106] record that partial bilateral removal of the olfactory bulbs and tracts prevented infection from nasal instillation, and Schultz and Gebhardt [132] a similar finding after cauterization of these structures; in view of what follows, however, in respect to the recently studied virus of equine encephalomyelitis (*q.v.*), these observations can no longer be accepted as indicative of axonal spread unless it be shown that the operative procedure had not led also to cicatrization of the accompanying perineural lymphatics. Jungeblut and Spring [119] observed that after section of the spinal cord in the dorsal region, followed by intracerebral inoculation, poliomyelitis virus did not pass into the lower segments of the cord despite the fact that the circulation of cerebrospinal fluid was unimpeded. The occurrence of crossed paralysis noted by some observers [109, 131] after intracerebral inoculation has been denied by others [105].

O'Leary and his co-workers [126] dissent from the interpretation placed upon some of the foregoing observations. Using the cathode ray oscillographic technique they found that the functional activity of the nerve fibres of poliomyelitic animals remained normal until the period when histological changes were clearly demonstrable in the nerve cells. They believe that if the virus travelled by the axis cylinders signs of impaired conductivity should be manifest at an earlier stage; as an alternative they suggest that possibly the virus travels between the nerve fibres, and would explain Hurst's results after sciatic inoculation on the ground that the path of least resistance lies between the pyramidal fibres rather than across them. It is probably impossible finally to prove or disprove this hypothesis, which in this case rests upon the assumption that the passage of virus along the axon is necessarily detrimental to that structure. This by no means follows from the evidence available. In several diseases due to neurotropic viruses it is possible to detect nuclear inclusions, indicating deranged nuclear metabolism, while the cytoplasm is still normal; in pseudorabies in particular, the Nissl substance, Golgi apparatus, mitochondria and neurofibrils may appear unaltered with quite advanced nuclear changes [138]. It may be that the presence of some viruses in the cytoplasm is relatively innocuous, and that it is by perversion of nuclear metabolism that impaired function of the cell and cytoplasmic degeneration are ultimately brought about. Were this so the conductivity of the axon would remain unaltered during transmission of the virus. On the other hand, in equine encephalomyelitis in which no evidence of axonal spread of the virus is yet forthcoming [56], the distribution of lesions in the brain at an early stage following intranasal instillation is in large part determined by the course of the olfactory connections.

Cowdry [8] finds the physical factors involved in the suggested spread by the axons difficult to comprehend. "The processes are tubes of capillary size through which no chemical substance could travel without being arrested by practically complete adsorption on the walls." He also quotes the observations of de Renyi (*loc. cit.*) on the consistency of nerve fibres. The fact referred to above, that the nucleus of the neuron is often the first part of the cell to show damage, suggests that the virus must enter and act upon the nucleus itself; thus the problem of passage of virus through a semi-solid gel cannot wholly be avoided, even though minimized by the assumption that penetration of the cytoplasm does not occur until the cell body is reached. Except for this difficulty in explaining transmission, if viruses are obligatory intracellular parasites we might anticipate penetration of the neuron at the nearest point, i.e. in the case of peripheral inoculation at the nerve ending or exposed part of the axon, which after all is merely an extension of the cell body. In certain circumstances the alternative to axonal spread, viz. transport by the perineural lymphatics, is at least as difficult to envisage; in the case of a strictly neurotropic virus, such as that of rabies which does not multiply at the site of inoculation (personal observation), after introduction of a small amount by scarification we should have to postulate a regular fluid flow capable of delivering the virus without loss from the site of infection all the way from the nerve endings to the cord.

Levaditi imagines the propagation of viruses as taking place by infection of successive segments of the axon accompanied by the development of immunity and a refractory state in the parts previously affected (neuroprobasia, [69]). It seems, however, that this is pure hypothesis without adequate experimental basis. It has been shown [115] that in poliomyelitis excision of the sciatic nerve from the sciatic foramen downwards, within twenty-four hours of intraneural inoculation at the level of the popliteal fossa, prevents development of the disease, whereas the same procedure at thirty-six hours does not; Koppisch [68] has criticized this observation, partly on the ground that trauma may completely alter the rate of conduction of virus along the nerve, but his own figures for the rate of transmission of herpes virus, 0·35 mm. per hour, are not vastly different. If they represent the speed of transmission of a virus, it is difficult to see how any immunity reaction, in the accepted sense of the term, could be evoked in so short a period of time. On the other hand, if, as seems doubtful, Yuien's experiments (*loc. cit.*) can be taken at their face value, this time is greatly in excess of that required for solutions to pass along the perineural lymphatics.

To conclude, the available evidence clearly establishes the importance of the neural path in infections of the central nervous system with the neurotropic viruses. It does not favour the belief that in the transport of virus the perineural lymphatics and cerebrospinal fluid take the major part; with Pette, Demme and Környey [129], however, we are far from denying that the fluid may at some stage play a subsidiary rôle. On the other hand a number of observations strongly suggest the possibility of transmission along the axis cylinders of the nerve trunks; the chief difficulty in the general acceptance of this belief lies in the physical constitution of the nerve fibre. It is obvious that much more work is needed to reconcile conflicting statements regarding the finer anatomy of the nerve trunks and the structure of the nerve fibre before universal agreement is obtained.

The Presence of Virus in the Blood-stream.

The nervous tissues are separated from the blood-stream by physiological barriers, the blood-brain and blood-cerebrospinal fluid barriers, which hold back many substances of even comparatively simple structure and low molecular weight. Most bacterial toxins and many dyes are thus prevented from reaching the nerve cells, though in this connection the electrical charge is possibly important [11]; antibodies also do not pass the barriers. It is not difficult to believe that circulating viruses, especially the larger ones, would likewise be denied direct access to the nervous structures, though it might equally readily be supposed that some might ultimately "grow through" the barrier by infecting the cellular elements concerned. The limited evidence available suggests that viruses do not easily penetrate the barrier. Thus McKinley and Holden [21] found that bacteriophage did not appear in the cerebrospinal fluid within twenty-four hours of intravenous inoculation. On the other hand, these authors claimed that the virus could pass in the opposite direction, from fluid to blood.; in this case the effect on the permeability of the barrier of intrathecal inoculation of foreign material was not excluded as the essential factor, though Flexner and Amoss [110, 111] had previously demonstrated its operation in experimental poliomyelitis. Klieneberger [12·5] found only slight penetration of the barrier when enormous doses of bacteriophage were given intravenously. The virus of equine encephalomyelitis, of comparatively small size, and the larger pseudo-rabies virus do not pass directly from blood to cerebrospinal fluid or nervous tissues [56, 139].

There is, of course, an abundant literature on the means whereby permeability of the barriers may be increased. In work with viruses slight trauma is often deliberately inflicted to circumvent the normal defence mechanism. Winkler [210] stated that vaccinial infection increases permeability to the bacteriophage. Le Fèvre de Arric and Millet [13-15] claimed to have favoured penetration by intraspinous inoculation of distilled water or hypertonic saline, and by intravenous injection of various chemicals and dyes; they worked, however, with viruses (herpes, rabies) which in untreated animals may under certain conditions produce nervous disease following intravenous inoculation. Demme [8·5] found that pathological conditions of the meninges and brain favoured the passage of bacteriophage from the blood.

In determining the rôle played by the blood in infections with the neurotropic viruses two considerations must be borne in mind. In the first place the same importance cannot be attached to the presence of virus in the circulating fluid at all stages of infection. Thus it would not be remarkable if on occasion in the later stages of a particular disease, coincidently with lysis and phagocytosis of destroyed nerve cells, positive blood tests were recorded. Of quite different significance would be the circulation, during the incubation period, of virus inoculated intranasally or intramuscularly, though, as will be seen presently, precocious infectivity of the blood is not necessarily a pointer indicating the route of invasion of the central nervous system.

The second consideration concerns the clearing mechanism of the blood. Viruses inoculated intravenously are, no doubt, dealt with in the same way as are visible bacteria. Within a few hours of inoculating a large dose of equine encephalomyelitis virus, none may be detected in the blood [56]. A large dose of pseudorabies virus so introduced disappears even more rapidly [139]; later, after the virus has undergone considerable multiplication in various viscera, the blood once more becomes infective. In some cases after subcutaneous inoculation of pseudorabies virus the lung and spleen may be infective when passage of the blood is negative, though, doubtless, this visceral virus has arrived by way of the circulation. These observations suggest that if a virus enters the circulation intermittently, even in considerable amounts, it is rapidly removed therefrom with restitution of sterility, and the blood infection remains inapparent; if passage of virus by way of the visceral nerves from the cord can be excluded, infectivity of the blood-rich organs may thus be a more delicate test for blood contamination than is afforded by single examination of the blood. The detection of virus in the blood must mean either that it is entering the circulation continuously and in considerable amount, or that it is growing in the blood, as Gordon suggests in the case of louping-ill [83], or else that the normal clearing mechanism is no longer operative; failure to detect virus signifies the exact converse and nothing more.

The facts bearing upon the part played by the blood may now be presented, and in doing this it is again convenient to consider separately the different classes of viruses.

The stricter neurotropes.—To recover poliomyelitis virus from the blood is unusual, though small quantities may be present at the height of the disease [102, 107, 112, 123, 136]; in any case positive results at an earlier stage would probably have little significance in the pathogenesis of the nervous disease, since only with very large doses does intravenous inoculation lead to infection [107], and inoculation directly into the carotid artery is no more successful [118].

Rabies virus, too, is rarely found in the blood [150]; moreover, the criteria of infection in the passage animals of some of the earlier workers who claimed positive results would probably not now be accepted. Even if virus does occasionally appear in the blood, Schweinburg and Windholz' experiments [189] seem to show that the occurrence is without bearing on the invasion of the nervous system; into one animal of each of eighteen pairs of parabiotic guinea-pigs they inoculated rabies virus, and only the inoculated animals developed the disease.

Using reasonable amounts of virulent emulsion, most authors have found intravenous inoculation ineffective, though possibly different animal species vary somewhat in their response [150]. Schweinburg [188] states that to ensure positive results it is not always necessary, as Jowelew [164] maintains, to break down the hæmato-encephalic barrier by "pumping"; in the guinea-pig 90 per cent. success is attained with large quantities of thick emulsion freed by paper-filtration from coarse particles. But the dosage needed amounts to 6 c.c. per kilo body-weight! Hurst (work to be published) has recently found that intravenous inoculation of virulent guinea-pig brain in the rabbit is much more effective than is that of homologous brain, and that infection is secured with quite small doses; the reason for this is at present under investigation.

Borna virus is not found in the blood [42]; Seifried [25] regards as exceptional Ernst and Hahn's results [39], in which virus was not only detected therein, but also passed through the placenta to the fœtus. Single intravenous inoculations are stated not to produce the disease

[40, 42], though the writer has sometimes been successful with large doses.

Practically no work has been undertaken to elucidate the method of infection of the central nervous system in the case of successful intravenous inoculation of viruses of this type. The one important observation is that of Lennette and Hudson [124] who found that repeated intravenous injection of poliomyelitis virus was ineffective if the monkeys were previously subjected to extirpation of the olfactory bulbs and tracts. Since they also found that following injection virus might be present in the nasal washings, the path of infection seems obvious. As will be seen later, work along other lines led the writer to a similar conclusion in the case of the equine encephalomyelitis virus.

The pantropic viruses.—These may or may not be detected with ease in the blood-stream.

In this respect the virus of pseudorabies is not consistent in its behaviour. During and for some time prior to the period of nervous symptoms in rabbits infected with the Aujeszky strain, the blood is usually infective in high dilution [142, 144, 147], though this may not have been so when the virus was first isolated [137, 139, 141, 143]. On the other hand, the serologically identical Iowa strain [146] is inconstantly present in even large volumes of blood [139, 145], though possibly with repeated passage this difference between it and the classical strain is less marked. Be this as it may, the observation that after subcutaneous or intramuscular inoculation virus and lesions first appear in the nervous system at the level directly connected with the site of inoculation [139] demonstrates that the blood is not the medium of transport to the cord, which, as with viruses of the preceding group, is invaded by way of the peripheral nerves. After intravenous inoculation virus appears in the nervous tissues no sooner than after subcutaneous or intramuscular injection; the fact that, in contrast to the stricter neurotropes, this virus infects very readily by the intravenous route must be related to its pluricellular affinities permitting it to establish infective foci in certain viscera, from which follows extension by the neural route. For the same reason virus introduced into a denervated area proliferates locally, invades the blood-stream, infects the general viscera, and ultimately reaches the nervous system by the visceral nerves [139].

The virus of herpes may sometimes be detected in the blood [69, 73], but, as already detailed, infection of the brain takes place through neural agency. Intravenous inoculation often leads to foci of necrosis in the adrenals and liver [67, 75, 76], which presumably form the starting point for the not infrequent invasion of the nervous system [61, 67, 73, &c]. Local growth of virus followed by a non-apparent infection of the blood-stream, as suggested in the introduction to this section, might account for Marinesco and Draganesco's observation that crushing a peripheral nerve so as to interrupt completely the axons between the site of intraneural inoculation and the cord did not prevent the nervous infection [20] ; these authors accept this finding as evidence of spread of the virus by the perineural spaces. Usually, inoculation into a denervated area does not lead to nervous involvement [67, 69].

The B. virus has not yet been detected in the blood [36], but the presence of numerous necrotic foci in the viscera at an early stage after intratesticular inoculation [37], and less frequently with other routes of infection, are certain proof of blood contamination, apparent or inapparent. Just as with pseudorabies virus, intravenous inoculation of even small doses leads to the nervous disease. The histological and clinical findings certainly indicate neural spread to the nervous system.

The state of affairs with some other pantropic viruses (equine encephalomyelitis, yellow fever,[1] and louping-ill viruses) is quite different. At death following inoculation by a peripheral route, virus and lesions are usually localized to the nervous system, leaving the blood virus-free. But before the period of nervous manifestations these viruses may undergo considerable multiplication outside the nervous system, and the blood is often highly infective. It may be noted that in Nature these diseases are transmitted by the bites of blood-sucking insects [57-58·5, 86].

From the point of view of the mechanism of infection of the central nervous system, the virus of equine encephalomyelitis has perhaps been studied most completely. Introduced in even small doses intravenously or by some other route of peripheral inoculation [56], this virus appears sooner or later in the blood where its titre rapidly rises. After a time in the monkey virus disappears from the blood, and humoral immunity, as judged by the presence of neutralizing antibodies in the serum, is established ; the animal may thereafter remain well. But in about half the cases, when the monkey provides as potent an antiserum as it ever will, it develops encephalitis and dies. In the case of the guinea-pig a much higher percentage of animals contracts the nervous disease and dies, and the nervous phase follows much more quickly on the visceral, occurring perhaps before the blood is wholly virus-free. There is no evidence that infection of the nervous system takes place by way of the peripheral nerves in general; after inoculation intramuscularly, intradermally or intraneurally in the hind limb, virus and lesions do not appear first in the lumbar cord or intervertebral ganglia. In the monkey the cerebrospinal fluid is infective before many parts of the brain tissue, but after intravenous inoculation of large doses of virus several days elapse before the fluid becomes virulent, ruling out the possibility of direct passage through the blood-cerebrospinal fluid barrier. In the guinea-pig the frontal region of the brain is almost always virulent before the brain-stem and cord, as it is, though at an earlier stage of infection, after intranasal instillation of virus. During the period of blood-circulation of virus following intramuscular inoculation, virus may appear in the nasal washings; while in a certain number of cases, but not in all, after intramuscular inoculation the distribution of lesions is similar to that obtaining after intranasal instillation. In short, after inoculation by the intramuscular and similar routes the evidence points to a spread of virus from the blood to the nasal mucosa and thence to the brain as the most frequent occurrence.

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[1] The differences between the ordinary "viscerotropic" yellow fever virus and the modified "neurotropic" strain are not as great as was formerly supposed. Theiler and Hughes [224] have shown that African monkeys said to be insusceptible to the viscerotropic virus may develop encephalitis on intracerebral inoculation, as do Asiatic monkeys in which the attack on the liver is frustrated by administration of antiserum. Similar observations are recorded by Findlay and Stern [217 5]. One variant may readily be converted into the other [216]. Thus the term "viscerotropic" has here a meaning different from that given in this review.

Now since there is no evidence in favour of neural spread after intramuscular or intrasciatic inoculation, it does not seem likely that virus is transported from the nose by the fibrils of the olfactory nerve; the work already cited [3, 7, 30, 31, 34] suggests an alternative and more probable path by the perineural lymphatics accompanying the nerve. If this latter is the route utilized, there is no apparent reason why virus introduced into the sciatic nerve should not travel to the cord by the perineural lymphatics, unless these structures in the case of the peripheral nerves do not connect centrally with the subarachnoid space; the above observations, therefore, offer some support to the anatomical evidence that no direct connection exists. This conclusion in turn implies that such viruses as do pass along the peripheral nerves to the nervous axis, as poliomyelitis, rabies, &c., attain their objective by the medium of the axis cylinders.

It might be thought possible by experimenting with animals previously subjected to ablation of the olfactory bulbs to prove definitely that virus travels from blood to brain by way of the nose, especially as it seems likely that cicatrization following the operative procedure would block also the lymphatic connections. Unfortunately, the impaired efficiency of the hemato-encephalic barrier following trauma to the nervous tissue persists for a very long time. It follows that with viruses circulating in the blood only negative results such as those obtained by Lennette and Hudson with poliomyelitis would be of significance. In the case of equine encephalomyelitis, infection of the nervous system still followed intramuscular inoculation in animals subjected two months previously to the operation indicated, though other observations suggested that the direct route from nose to brain had been blocked [56].

Occasionally after intramuscular inoculation of the virus of equine encephalomyelitis, the brain-stem and not the frontal region first becomes infective. Also, since the distribution of lesions following intramuscular inoculation is not always identical with that after intranasal instillation, we cannot assert that the path suggested above is the only one possible. On theoretical grounds it can be imagined that the virus may "grow through" the blood-brain barrier. During the phase of visceral infection the cells constituting the barrier may be infected, and virus may persist in them, as it does in the spleen, for some time after antibodies have appeared in the blood. Once immunity is established, virus escaping on the blood side of the barrier would be impotent in the presence of antibodies and resistant tissues, whereas virus leaking on the other side would find itself in a susceptible tissue shut off from humoral influences by the barrier; a fatal encephalitis might then ensue in spite of the visceral immunity. That this course of events is possible is shown by the observation that while a monkey which has passed the visceral phase of infection without having developed encephalitis will tolerate millions of infective doses of virus inoculated intramuscularly, it usually contracts encephalitis and dies if virus be inoculated directly into the brain [56].

Many of the facts established concerning the viruses of louping-ill [81-84, 87] and yellow fever [214, 215, 219, 220, 224] would fit in with the assumption that their mode of action is essentially similar to the foregoing, though it must be mentioned that Theiler [222, 223] has obtained apparently definite evidence of neural spread of yellow fever virus. There are, however, considerable gaps in our knowledge concerning these other viruses; a full discussion has been published elsewhere [56].

To conclude, detection of a neurotropic virus in the blood is likely only when the virus is entering the circulation more or less continuously and in large amounts, i.e. when large reservoirs of virus exist in the tissues, or if it is actually growing in the blood. It is, therefore, unusual to find the stricter neurotropes in the blood, at least until the terminal stages of the nervous infection. The pantropic viruses appear more frequently, especially the equine encephalomyelitis—yellow fever—louping-ill group in which a period of blood infection is a characteristic feature of the pre-nervous phases of the disease and allows of transmission of the contagium by blood-sucking insects. From a pathogenetic standpoint the significance of virus in the blood lies not in the immediate consequences, for the normal hæmato-encephalic barrier is probably impervious to most if not all viruses, but in the possible distribution of virus to areas from which the nervous system may be infected. In the case of some pantropic viruses infective visceral foci are thus established from which ascent to the nervous system by the neural route may follow. Other viruses appear on the nasal mucosa and reach the nervous system by the olfactory nerve or, more probably, by its accompanying lymphatics. The possibility of a slow "growth through" the hæmato-encephalic barrier, due to infection of its constituent cells by a virus, must also be considered, though at present there is no certain evidence of such an occurrence.

A SUGGESTED BASIS FOR CLASSIFICATION OF VIRUSES AFFECTING THE NERVOUS SYSTEM.

Even though our knowledge is far from complete, it is permissible to attempt a classification of the known facts provided that the possibly temporary nature of the edifice be clearly recognized. Though ultimately modified or discarded, it serves for a time as a framework within which new findings may be more readily compared or contrasted with old. The following purely tentative grouping of the viruses discussed above is suggested.

Group 1. *The stricter neurotropes.*—These attack directly and destroy nerve cells, central and peripheral, but are without obvious direct action on other cells; the inflammatory reaction in the nervous tissues is purely secondary and reactive. They do not multiply except in nervous tissue. Introduced at a peripheral site they pass up the local nerves to the central nervous system; inoculated into a denervated area no disease results. They are rarely found in blood or cerebrospinal fluid, at any rate until late in the nervous disease; intravenous inoculation of moderate to small doses is usually ineffective. Examples are the viruses of poliomyelitis, rabies, pseudorabies (in the monkey), and Borna disease.

Group 2. *The pantropic viruses, Type* 1.—While definitely neurotropic, these also directly attack and produce specific lesions in cells derived from all embryonic layers. In the nervous system, consequently, they attack both ectodermal and mesodermal structures ; in the viscera they may produce multiple foci of necrosis. They grow with greater or less facility in situations outside the nervous system, as well as in the brain and cord. They may or may not be easily detected in the blood; if not, indirect evidence of blood spread is often forthcoming, but invasion of the nervous system is by way of the peripheral nerves. Inoculation into a denervated area often leads to the nervous disease; in these cases local growth followed by blood contamination allows the virus to set up infective visceral foci from which follows invasion of the nervous system by the visceral nerves. Intravenous inoculation of small doses is often effective. Examples are the virus of herpes febrilis (in the rabbit, &c.), that of pseudorabies (in the rabbit), and the B. virus ; the herpes virus is probably nearer the stricter neurotropes than are the other two.

Group 3. *The pantropic viruses, Type* 2.—Although these viruses as a group are pantropic, the cellular affinities of individual representatives are more restricted than with viruses of Type 1 ; outside the nervous system they are directed particularly to epithelial and blood-vascular structures. Characteristically, a phase of blood infection is followed by systemic immunity ; in a certain proportion of cases encephalitis supervenes after the virus has disappeared from the blood, and when presumably the body as a whole already is, or is becoming, immune. Intravenous inoculation is often successful with small doses. Many of these diseases are spread in nature by blood-sucking insects. In the case of one of these viruses, that of equine encephalomyelitis, no evidence of neural spread is forthcoming; during circulation in the blood, virus appears on the nasal mucosa and reaches the brain probably by the perineural lymphatics of the olfactory nerves. Further investigation is needed to show whether such behaviour is typical of the group. In the nervous system there is a primary and direct attack on the nervous elements. Examples are the viruses of equine encephalomyelitis, yellow fever, louping-ill, and vesicular stomatitis.

Group 4. *The viscerotropic viruses.*—For want of a better, this term is applied for the time being to certain viruses which, under conditions of natural infection, are not excitants of encephalitis. The lesions they promote on inoculation directly into the brain are primarily meningeal, and there is no evidence of damage of nerve cells of greater degree than accompanies any meningitis of corresponding severity. Examples are the viruses of vaccinia, lymphogranuloma inguinale and salivary-gland disease of guinea-pigs.

A NOTE ON THE SELECTIVE DISTRIBUTION OF NERVOUS LESIONS DUE TO CERTAIN VIRUSES.

One of the most fascinating and at the same time difficult problems confronting the neuropathologist is that of the selective localization of certain morbid processes to given regions of the nervous system. Vogt [33, &c.] seeks to account for many examples of such distribution of lesions on his theory of "pathoclisis," which implies a vulnerability of certain nervous elements inherent in their physicochemical structure. While this assumption, which in one sense seeks to explain the unknown in terms of the unknown, is sometimes unavoidable, it must obviously be made with caution, for time may reveal the participation of determinant factors at present obscure and unconnected with the constitution of particular types of cell. The valuable contributions of Spielmeyer and his pupils [4, 27, 28, 32, &c.] have, for instance, emphasized the importance in some cases of the vascular factor in this connection, though Spielmeyer clearly recognized that it is not always or solely operative. In the realm of virus diseases we meet with several examples of a constant or very frequent elective localization of the most severe lesions, and since we know almost nothing of the underlying causes we must not rashly conclude that in all instances these are of the same nature.

In many diseases of the nervous system due to viruses the seat of maximal pathological changes is in large part dependent upon the site of inoculation or on the route of natural entry of the virus. Thus, inoculated intracerebrally into the rabbit, the B. virus gives rise to an encephalomyelitis with generalized hyperæsthesia, salivation, convulsions and speedy exitus as the cardinal clinical features; on the other hand, inoculated intramuscularly or intradermally in the flank or leg it is responsible for an acute ascending myelitis with death delayed for several days, and cerebral involvement is minimal both clinically and pathologically [37, 38]. Again, speaking quite generally of rabies in the monkey, more intense changes are found in the cord after intrasciatic inoculation than after intracerebral, while higher levels suffer more severely under the reverse circumstances [163].

By way of contrast, in poliomyelitis in both man and monkey the anterior horns of the cord show maximal involvement whether the virus is introduced intranasally, intracerebrally, or intraneurally. In the motor cortex, often the only cortical area to show damage, cellular infiltration occurs in several laminæ, though opinions differ as to whether the Betz cells are or are not electively destroyed [114, 120, 133]; in the brain-stem neither motor nor sensory nuclei are consistently picked out [133]; in the cord destruction is not absolutely limited to the motor cells [114, 133]. It is inaccurate, therefore, to speak of a pure attack on the motor system [133]; nevertheless, in the cord at any rate, it is the motor nerve cells which are predominantly affected. *In the present state of our knowledge* there appears to be no reason for this unless we assume especial vulnerability of these neurons to the infective agent [114].

An analogous occurrence is seen in louping-ill in the monkey. Whereas in the sheep and the mouse some destruction of Purkinje cells is apparent, and in the mouse the granular layer of the cerebellum may also suffer severely, in the monkey an almost complete, elective disappearance of Purkinje cells follows infection by the intracerebral [80, 85], intrasciatic (personal observation), or intranasal route [82]. Lesions are always present in other parts of the brain, but in no one region are they as severe, or present with such constancy, as in the Purkinje-cell layer.

Thirdly, whether introduced into the brain, the cisterna magna or the sciatic nerve, the virus of pseudorabies exerts its chief action in the monkey on certain cortical areas, though within these areas the major incidence is not on a single type of nerve cell and the glia also is specifically involved [140]. More so than in the preceding instances, there seems here to be an elective attack on given areas as areas, without regard to the precise distribution of a particular kind of neuron.

The relative frequency with which Negri bodies are found in the cornu Ammonis, and some other situations [177], in rabies is accepted by many authors as indicative of greater resistance, due to physico-chemical or developmental factors, of the neurons of this part of the brain [170, 174, 175, &c.]; the nerve cells in question are otherwise relatively normal [186], while destruction of nerve cells and neuronophagia occur in parts where Negri bodies are seen less often.

Among themselves nerve cells differ in certain obvious respects, in size and shape, in the form in which their tigroid substance is precipitated by fixatives, in the number of mitochondria in unit volume, and so on; of possibly more fundamental and significant differences in constitution we have at present little information. If, *faute de mieux*, in relation to the foregoing observations we postulate differences in structure or metabolism of the different types of neuron, we must not forget that the existence of such differences is largely hypothetical and must remain so until biochemistry can show in just what respect a motor differs from a sensory neuron. It is interesting, however, to note the analogy of the apparent affinity of some viruses for a particular kind of nerve cell to the extraordinarily specific action on a single type of cell of some of the fowl-tumour viruses, or again to the intimate relation between chemical structure in various phenol esters and their remarkably selective action on certain nervous structures [19].

There is one more problem of localization to be mentioned. While it would be far from exact to state that the symptomatology of different diseases due to neurotropic viruses in the smaller laboratory animals is indistinguishable except on the basis of acuteness or otherwise, it is a fact, comprehensible in view of the lesser complexity of the brains of these creatures, that in them the clinical pictures of the various infections are less characteristic than in the higher mammals. As an example, louping-ill and yellow fever induce not dissimilar syndromes in the mouse, differing rather in duration than in the symptoms exhibited. On the contrary, in the monkey the clinical manifestations of the various virus diseases studied by the writer have been highly distinctive and could not readily be confused one with another. Since symptoms reflect merely the localization of lesions, in the lower animals we should anticipate less diverse distribution of the major pathological changes.

Experience has shown that in a number of neurotropic virus diseases of the mouse, guinéa-pig and rabbit the outstanding lesion is often massive acute necrosis in the cornu Ammonis and in the rhinencephalic cortex ventral to the *fissura rhinica*; large stretches of pyramidal cells may here be destroyed *in toto*. Lentz first described the eosinophilic, shrunken nerve cells with their pyknotic and fragmented nuclei as characteristic of passage rabies and called them "Passagewutkörperchen" [169], though they had been seen previously by Achúcarro [148], and have, apparently, been re-discovered by Levaditi and his colleagues [169·5]; they occur also in rabbits infected with street virus [163]. Similar appearances obtain in mice with louping-ill [85], yellow fever and St. Louis encephalitis [200], in rabbits with herpetic and virus III infections [212], and in guinea-pigs with equine encephalomyelitis [55]. In the corresponding diseases of higher animals, as the dog, cow, horse, monkey, although foci of destruction of nerve cells may be observed in these situations, the writer has so far not seen massive necrosis of the kind under consideration; only in pseudorabies in the monkey is the cornu Ammonis affected almost as a whole, and then as only part of the elective distribution of lesions already mentioned. This phenomenon, common to the action of many viruses, is evidently of a different order from the apparently specific affinity between one virus and a given cell system, as in poliomyelitis. It must be regarded not so much as the outcome of a particular virus—host reaction, as the general response of a certain type of host to neurotropic viruses in general. The type of host appears to be that in which the olfactory brain is, relatively speaking, most highly developed, and is presumably relatively more abundantly supplied with fibre connections from other centres. On a previous occasion [55], the opinion was expressed that if the neurotropic viruses spread along axis cylinders we may offer an explanation in terms of the probable amount of virus reaching the affected areas. It has since appeared unlikely that, of those mentioned above, the virus of equine encephalomyelitis is transmitted by the axis cylinders [56]; nevertheless, as we have seen, after intranasal inoculation, or what in many cases amounts to the same thing after intramuscular or subcutaneous inoculation, the distribution of lesions in the brain at an early stage of infection is governed in large part by the central connections of the olfactory nerves. Whatever the correct explanation, it is obvious that this problem of localization of morbid changes is wholly different from that in poliomyelitis and louping-ill.

REFERENCES.

General References and Reviews.

[1] Abel, J. J. *Science*, 1934, **79**, 63 and 121.
[2] Abel, J. J., Evans, E. A., Hampil, B., and Lee, F. C. *Bull. Johns Hopkins Hosp.*, 1935, **56**, 84.
[3] André, J. M. "Contribution à l'étude des Lymphatiques du Nez et des Fosses Nasales." Paris. 1905.
[4] Bodechtel, G. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1930, **123**, 485.
[5] Boemke, F. *Virch. Arch. f. path. Anat.*, 1934, **293**, 180.
[6] Carmichael, E. A. *Journ. Neurol. and Psychopath.*, 1929, **9**, 209.
[7] Clark, W. E. le Gros. Reports on Public Health, No. 54. H.M. Stationery Office, London. 1928.
[8] Cowdry, E. V. *Arch. Path.*, 1934, **18**, 527.
[8·5] Demme, H. *Deut. Zeit. f. Nervenheilk.*, 1933, **130**, 88.
[9] De Renyi, G. S. In "Special Cytology." Edited by E. V. Cowdry, vol. 3, p. 1370. New York. 1932.
[10] Elman, R. *Bull. Johns Hopkins Hosp.*, 1923, **34**, 99.
[11] Friedemann, U., and Elkeles, A. *Lancet*, 1934 (1), 719, 775.
[12] Horster, H., and Whitman, L. *Zeit. f. Hyg. u. Infektionskr.*, 1932, **113**, 118.
[12·5] Klieneberger, E. *Arch. f. exp. Path. u. Pharmakol.*, 1931, **161**, 485.

[13] Le Fèvre de Arric, M., and Millet, M. *C.R. Soc. Biol.*, 1925, **93**, 45.
[14] *Idem.* *Ibid.*, 1926, **94**, 782.
[15] *Idem.* *Ibid.*, 1927, **96**, 206.
[16] Levaditi, C. *C.R. Soc. Biol.*, 1921, **85**, 425.
[17] *Idem.* *Ann. Inst. Past.*, 1930, **45**, 673.
[18] Levaditi, C., Lépine, P., and Schoen, R. *Ibid.*, 1929, **43**, 1465.
[19] Lillie, R. D., and Smith, M. I. National Inst. of Health, Bull. 160. U.S. Treasury Dept., Washington. 1932.
[20] Marinesco, G., and Draganesco, S. *Rev. Neurol.*, 1932 (1), 1.
[21] McKinley, E., and Holden, M.. *Proc. Soc. Exp. Biol. and Med.*, 1927, **24**, 595.
[22] Nicolau, S., Nicolau, O., and Galloway, I. A. *Ann. Inst. Past.*, 1929, **43**, 1.
[23] Philibert, A. *Ann. Med.*, 1924, **16**, 283.
[24] Rivers, T. M. *Amer. Journ. Path.*, 1928, **4**, 91.
[25] Seifried, O. *Ergeb. allg. Path. u. path. Anat.*, 1931, **24**, 554.
[26] Seifried, O., and Spatz, H. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1930, **124**, 317.
[27] Spielmeyer, W. *Ibid.*, 1925, **99**, 756.
[28] *Idem.* *Ibid.*, 1928, **118**, 1.
[28·5] Sullivan, W. E., and Mortensen, O. A. *Anat. Rec.*, 1934, **59**, 493.
[29] Thiele, F. H., and Embleton, D. *Proc. Roy. Soc. Med.*, 1914, **7**, Path. Sect., 68.
[30] Turner, A. L., and Reynolds, F. E. *Journ. Laryngol. and Otol.*, 1926, **41**, 717.
[31] *Idem.* *Ibid.*, 1927, **42**, 525.
[32] Uchimura, J. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1928, **112**, 1.
[33] Vogt, O. *Journ. f. Psych. u. Neurol.*, 1925, **31**, 245.
[34] Weed, L. H. *Journ. Med. Res.*, 1914, **31**, 21.
[35] Yuien, K. *Fol. Anat. Jap.*, 1928, **6**, 301.

B. Virus.

[36] Sabin, A. B. *Brit. Journ. Exp. Path.*, 1934, **15**, 268.
[37] Sabin, A. B., and Hurst, E. W. *Ibid.*, 1935, **16**, 133.
[38] Sabin, A. B., and Wright, A. M. *Journ. Exp. Med.*, 1934, **59**, 115.

Borna Disease.

[39] Ernst, W., and Hahn, H. *Münch. tierärzt. Wchnschr.*, 1927, **78**, 85.
[40] Nicolau, S., and Galloway, I. A. Medical Research Council Report, No. 121, H.M. Stationery Office, London. 1928.
[41] Nicolau, S., Galloway, I. A., and Nicolau, O. *C. R. Soc. Biol.*, 1928, **99**, 674.
[42] Zwick, W., Seifried, O., and Witte, J. *Zeit. f. Infektionskr. Haust.*, 1927, **30**, 42.
[43] *Idem.* *Arch. f. wiss. u. prakt. Tierheilk.*, 1929, **59**, 511.

Dog Distemper.

[44] Babes, V., and Starcovici, C. *C. R. Soc. Biol.*, 1912, **73**, 229.
[45] Cerletti, U. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1912, **9**, 520.
[46] Dunkin, G. W., and Laidlaw, P. P. *Journ. Comp. Path. and Therap.*, 1926, **39**, 201, 213.
[47] Gallego, A. *Zeit. f. Infektionskr. Haust.*, 1928, **34**, 38.
[48] Marinesco, G., Draganesco, S., and Stroesco, G. *Ann. Inst. Past.*, 1933, **51**, 215.
[49] Perdrau, J. R., and Pugh, L. P. *Journ. Path. and Bact.*, 1930, **33**, 79.
[50] Sanfelice, F. *Cent. Bakt.*, Abt. 1, Orig., 1915, **76**, 495.

Epizootic Fox Encephalitis.

[51] Green, R. G., Katter, M. S., Shillinger, J. E., and Hanson, K. B. *Amer. Journ. Hyg.*, 1933, **18**, 462.
[52] Green, R. G., Ziegler, N. R., Carlson, W. E., Shillinger, J. E., Tyler, S. H., and Dewey, E. T. *Ibid.*, 1934, **19**, 343.
[53] Green, R. G., and Shillinger, J. E. *Ibid.*, 1934, **19**, 362.
[54] Levaditi, C., Lépine, P., Bazin, J., and Schoen, R. *C. R. Soc. Biol.*, 1930, **104**, 755.

Equine Encephalomyelitis.

[55] Hurst, E. W. *Journ. Exp. Med.*, 1934, **59**, 529.
[56] *Idem.* *Journ. Path. and Bact.*, 1936, **42**, 271.
[57] Kelser, R. A. *Journ. Amer. Vet. Med. Assoc.*, 1933, **82**, 767.
[58] Merrill, M. H., Lacaillade, C. W., and TenBroeck, C. *Science*, 1934, **80**, 251.
[58·5] Merrill, M. H., and TenBroeck, C. *Journ. Exp. Med.*, 1935, **62**, 687.

Herpes Febrilis.

[59] Da Fano, C. *Journ. Path. and Bact.*, 1923, **26**, 85.
[60] Da Fano, C., and Perdrau, J. R. *Ibid.*, 1927, **30**, 67.
[61] Doerr, R., and Vöchting, R. *Rev. gén. Ophth.*, 1920, **34**, 409.
[62] Flexner, S., and Amoss, H. L. *Journ. Exp. Med.*, 1925, **41**, 215.
[63] *Idem.* *Ibid.*, 1925, **41**, 357.
[64] Goodpasture, E. W. *Amer. Journ. Path.*, 1925, **1**, 1.
[65] *Idem.* *Ibid.*, 1925, **1**, 11.
[66] Goodpasture, E. W., and Teague, O. *Journ. Med. Res.*, 1923, **44**, 121.
[67] *Idem.* *Ibid.*, 1923, **44**, 139.
[68] Koppisch, E. *Zeit. f. Hyg. u. Infektionskr.*, 1935, **117**, 386.
[69] Levaditi, C. *L'Herpès et le Zona*, Paris, 1926.
[70] Marinesco, G., and Draganesco, S. *Ann. Inst. Past.*, 1923, **37**, 753.
[71] Pette, H. *Verhandl. d. Gesellsch. deut. Nervenärzte*, 1926, 207.
[72] *Idem.* *Deut. Zeit. f. Nervenheilk.*, 1931, **121**, 113, 143; **122**, 209, 221.
[73] Remlinger, P., and Bailly, J. *C. R. Soc. Biol.*, 1925, **93**, 1071.
[74] Rose, G., and Walthard, B. *Zeit. f. Hyg. u. Infektionskr.*, 1926, **105**, 645.
[75] Smith, W. *Journ. Path. and Bact.*, 1931, **34**, 493.
[76] *Idem.* *Ibid.*, 1931, **34**, 747.

Hog Cholera.

[77] Seifried, O. *Journ. Exp. Med.*, 1931, **53**, 277.
[78] Seifried, O., and Cain, C. B. *Ibid.*, 1932, **56**, 345, 351.

Louping-Ill.

[79] Brownlee, A., and Wilson, D. R. *Journ. Comp. Path. and Therap.*, 1932, **45**, 67.
[80] Findlay, G. M. *Brit. Journ. Exp. Path.*, 1932, **13**, 230.
[81] Fite, G. L., and Webster, L. T. *Proc. Soc. Exp. Biol. and Med.*, 1934, **31**, 695.
[82] Galloway, I. A., and Perdrau, J. R. *Journ. Hyg.*, 1935, **35**, 339.
[83] Gordon, W. S. *Brit. Med. Journ.*, 1934 (i), 885.
[84] Gordon, W. S., Brownlee, A., Wilson, D. R., and MacLeod, J. *Journ. Comp. Path. and Therap.*, 1932, **45**, 106.
[85] Hurst, E. W. *Ibid.*, 1931, **44**, 231.
[86] MacLeod, J., and Gordon, W. S. *Ibid.*, 1932, **45**, 240.
[87] Pool, W. A., Brownlee, A., and Wilson, D. R. *Ibid.*, 1930, **43**, 253.

Lymphocytic Choriomeningitis.

[88] Armstrong, C., and Dickens, F. Pub. Health Rep., U.S. Treasury Dept., 1935, **50**, 831.
[89] Armstrong, C., and Lillie, R. D. *Ibid.*, 1934, **49**, 1019.
[90] Armstrong, C., and Wooley, J. G. *Ibid.*, 1935, **50**, 537.
[91] Rivers, T. M., and McNair Scott, T. F. *Science*, 1935, **81**, 439.
[92] Traub, E. *Science*, 1935, **81**, 298.

Lymphogranuloma Inguinale.

[93] D'Aunoy, R., Haam, E. von, and Lichtenstein, L. *Amer. Journ. Path.*, 1935, **11**, 737.
[94] Findlay, G. M. *Lancet*, 1932, (ii), 11.
[95] *Idem.* *Trans. Roy. Soc. Med. and Hyg.*, 1933, **27**, 35.
[96] Hellerström, S., and Wassén, E. Memorial Volume to Prof. J. Cantacuzène, Paris, 1934, 277.

[97] JONESCO-MIHAIESTI, C., TUPA, A., BADENSKI, G., and WISMER, B. *Bull. Acad. Med.*, 1933, **109**, 652.

[98] LEVADITI, C., RAVAUT, P., LÉPINE, P., and SCHOEN, R. *Ann. Inst. Past.*, 1932, **48**, 27.

[99] LEVADITI, C. *Bull. Acad. Med.*, 1933, **109**, 684.

POLIOMYELITIS.

[100] ABRAMSON, H. L. *Journ. Amer. Med. Assoc.*, 1917, **68**, 546.

[101] *Idem. Arch. Int. Med.*, 1918, **22**, 312.

[102] AMOSS, H. L. "In Filterable Viruses," edited by T. M. Rivers. Baltimore. 1928.

[103] ANDRÉ-THOMAS and LHERMITTE, J. *Rev. Neurol.*, 1929, **36** (1), 1242.

[104] BLANTON, W. B. *Journ. Med. Res.*, 1917, **36**, 1.

[105] BRODIE, M. Cited in "Poliomyelitis," International Committee for the Study of Infantile Paralysis. Baltimore, 1932, p. 290.

[106] BRODIE, M., and ELVIDGE, A. R. *Science*, 1934, **79**, 234.

[107] CLARK, P. F., FRASER, F. R., and AMOSS, H. L. *Journ. Exp. Med.*, 1914, **19**, 223.

[108] FABER, H. K., and GEBHARDT, L. P. *Ibid.*, 1933, **57**, 933.

[109] FAIRBROTHER, R. W., and HURST, E. W. *Journ. Path. and Bact.*, 1930, **33**, 17.

[110] FLEXNER, S., and AMOSS, H. L. *Journ. Exp. Med.*, 1914, **20**, 249.

[111] *Idem. Ibid.*, 1917, **25**, 525.

[112] FLEXNER, S., and CLARK, P. F. *Journ. Amer. Med. Assoc.*, 1911, **57**, 1685.

[113] HOWE, H. S. *Journ. Nerv. and Ment. Dis.*, 1918, **48**, 97 and 206; **50**, 409.

[114] HURST, E. W. *Journ. Path. and Bact.*, 1929, **32**, 457.

[115] *Idem. Ibid.*, 1930, **33**, 1133.

[116] *Idem. Ibid.*, 1932, **35**, 41.

[117] *Idem.* Cited in "Poliomyelitis," International Committee for the Study of Infantile Paralysis. Baltimore, 1932, p. 299.

[118] JUNGEBLUT, C. W. Cited in "Poliomyelitis," International Committee for the Study of Infantile Paralysis. Baltimore, 1932, p. 82.

[119] JUNGEBLUT, C. W., and SPRING, W. J. *Proc. Soc. Exp. Biol. and Med.*, 1930, **27**, 1076

[120] KÖRNYEY, ST. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1933, **146**, 724.

[121] LANDSTEINER, K., and LEVADITI, C. *Ann. Inst. Past.*, 1910, **24**, 833.

[122] LANDSTEINER, K., LEVADITI, C., and PASTIA, M. *Ibid.*, 1911, **25**, 804.

[123] LEINER, C., and VON WIESNER, R. *Wien. klin. Woch.*, 1909, **22**, 1698.

[124] LENNETTE, E. H., and HUDSON, N. P. *Proc. Soc. Exp. Biol. and Med.*, 1935, **32**, 1444.

[125] MARINESCO, G. *C.R. Soc. Biol.*, 1911, **70**, 286.

[126] O'LEARY, J. L., HEINBECKER, P., and BISHOP, G. H. *Arch. Neurol. and Psychiatr.*, 1932, **28**, 272.

[127] OLITSKY, P. K., RHOADS, C. P., and LONG, P. H. *Journ. Amer. Med. Assoc.*, 1929, **92**, 1725.

[128] PETTE, H. *Deut. Zeit. f. Nervenheilk.*, 1930, **116**.

[129] PETTE, H., DEMME, H., and KÖRNYEY, ST. *Ibid.*, 1932, **128**, 125.

[130] RISSLER, J. *Nord. med. Arkiv*, 1888, **20**, 1.

[131] RÖMER, P. H. "Die epidemische Kinderlähmung." Berlin. 1911.

[132] SCHULTZ, E. W., and GEBHARDT, L. P. *Proc. Soc. Exp. Biol. and Med.*, 1933, **31**, 728.

[133] SPIELMEYER, W. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1932, **142**, 159.

[134] WARBURG, B. *Arch. Neurol. and Psychiatr.*, 1931, **25**, 1191.

[135] WICKMAN, I. "Die akute Poliomyelitis bzw. Heine-Medinische Krankheit." Berlin. 1911.

[136] ZAPPERT, J., VON WIESNER, R., and LEINER, K. "Studien über die Heine-Medinische Krankheit." Leipzig u. Wien. 1911.

PSEUDORABIES.

[137] AUJESZKY, A. *Cent. Bakt.*, Abt. 1, Orig., 1902, **32**, 353.

[138] HURST, E. W. *Journ. Exp. Med.*, 1933, **58**, 415.

[139] *Idem. Ibid.*, 1934, **59**, 729.

[140] *Idem. Ibid.*, 1936. To appear in March number.

[141] Isabolinsky, M., and Patzewitsch, B. *Cent. Bakt.*, Abt. 1, Orig., 1912, **65**, 256.
[142] Remlinger, P., and Bailly, J. *C.R. Soc. Biol.*, 1933, **113**, 125.
[143] Sangiorgi, G. *Pathologica*, 1914, **6**, 282.
[144] Schmiedhoffer, J. *Zeit. f. Infektionskr. Haust.*, 1910, **8**, 383.
[145] Shope, R. E. *Journ. Exp. Med.*, 1931, **54**, 283.
[146] *Idem.* *Proc. Soc. Exp. Biol. and Med.*, 1932, **30**, 308.
[147] Zwick, and Zeller. *Arb. a. d. Kaiserlich. Gesundheits.*, 1911, **36**, 382.

RABIES.

[148] Achúcarro, N. *Nissl. u. Alzheimer's Arb.*, 1910, **3**, 143.
[149] Babes, V. *Ann. Inst. Past.*, 1892, **6**, 209.
[150] *Idem.* "Traité de la Rage." Paris. 1912.
[151] Bertarelli, E. *Cent. Bakt.*, Abt. 1, Orig., 1904, **37**, 218.
[152] Dawydowski, J. V., and Dwijkoff, P. P. *Verhandl. deut. path. Gesellsch.*, 1928, **23**, 427.
[153] Di Vestea, A., and Zagari, G. *Ann. Inst. Past.*, 1887, **1**, 492.
[154] *Idem.* *Ibid.*, 1889, **3**, 237.
[155] Duboué. "De la physiologie pathologique et du traitement rationnel de la rage." Paris. 1879. (Cited by Gamaleia.)
[156] Fedoroff, H. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1925, **100**, 248.
[157] Fermi, C. *Cent. Bakt.*, Abt. 1, Orig., 1907, **44**, 25.
[158] Gamaleia. *Ann. Inst. Past.*, 1887, **1**, 63.
[159] Gannt, W. H., and Ponomarew, A. W. *Zeit. f. d. ges. exp. Med.*, 1929, **66**, 582.
[160] Goodpasture, E. W. *Amer. Journ. Path.*, 1925, **1**, 547.
[161] Helman, M. C. *Ann. Inst. Past.*, 1889, **3**, 15.
[162] Herrmann, O. *Cent. Bakt.*, Abt. 1, Orig., 1925, **95**, 429.
[163] Hurst, E W., and Pawan, J. L. *Journ. Path. and Bact.*, 1932, **35**, 301.
[164] Jowelew, B. M. *Zeit. f. d. ges. exp. Med.*, 1930, **74**, 217.
[165] Kerbler, F. *Zeit. f. Hyg. u. Infektionskr.*, 1933, **115**, 235.
[166] Klarfeld, B. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1922, **77**, 80.
[167] Konradi, D. *Cent. Bakt.*, Abt. 1, Orig., 1922, **88**, 113.
[168] Krinitzky, S. I. *Virch. Arch. f. path. Anat.*, 1926, **261**, 802.
[169] Lentz, O. *Zeit. f. Hyg. u. Infektionskr.*, 1909, **62**, 63.
[169·5] Levaditi, C., Lépine, P., and Schoen, R. *C. R. Soc. Biol.*, 1929, **101**, 1050.
[170] Levaditi, C., Nicolau, S., and Schoen, R. *Ann. Inst. Past.*, 1926, **40**, 973.
[171] Levaditi, C., and Schoen, R. *C. R. Soc. Biol.*, 1933, **114**, 501.
[172] Lowenberg, K. *Arch. Neurol. and Psychiatr.*, 1928, **19**, 638.
[173] Manouelian, Y., and Viala, J. *C. R. Acad. Sci.*, 1928, **186**, 1242.
[174] *Idem.* *Ibid.*, 1928, **187**, 1168.
[175] Marinesco, G., and Stroesco, G. *Arch. Roum. Path. Exp.*, 1931, **4**, 243.
[176] Marinesco, G., and Draganesco, S., *Ann. Inst. Past.*, 1935, **54**, 299.
[177] Nicolau, S., and Kopciowska, L. *C. R. Acad. Sci.*, 1932, **194**, 1865.
[178] Nicolau, S., and Mateiesco, E. *Ibid.*, 1928, **186**, 1072.
[179] Nicolau, S., and Serbanescu, V. *C. R. Soc. Biol.*, 1928, **99**, 294.
[180] Repetto, R. *Cent. Bakt.*, Abt. 1, Orig., 1909, **49**, 457.
[181] Riesman, D., Fox, W. W., Alpers, B. J., and Cooper, D. A. *Arch. Int. Med.*, 1933, **51**, 644.
[182] Rojas, L. *Arch. f. Psychiatr.*, 1932, **96**, 1.
[183] Roux, E. *Ann. Inst. Past.*, 1889, **3**, 69.
[184] Schaffer, K. *Ibid.*, 1889, **3**, 644.
[185] *Idem.* *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1931, **136**, 547.
[186] Schiffman, J. *Zeit. f. Hyg. u. Infektionskr.*, 1906, **52**, 199.
[187] Schukri, L., and Spatz, H. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1925, **97**, 627.
[188] Schweinburg, F. *Zent. Bakt.*, Abt. 1, Orig., 1932, **124**, 426.
[189] Schweinburg, F., and Windholz, F. *Virch. Arch. f. path. Anat.*, 1930, **278**, 23.

[190] Slotwer, B. S. *Ibid.*, 1926, **261**, 787.
[191] Speransky, A. *Ann. Inst. Past.*, 1927, **41**, 166.
[192] Standfuss, R. *Arch. f. wiss. u. prakt. Tierheilk.*, 1908, **34**, 109.

Salivary Gland Virus of Guinea-Pigs.

[193] Andrewes, C. H. *Brit. Journ. Exp. Path.*, 1930, **11**, 23.
[194] Cole, R., and Kuttner, A. G. *Journ. Exp. Med.*, 1926, **44**, 855.
[195] Hudson, N. P., and Markham, F. S. *Ibid.*, 1932, **55**, 405.
[195·5] Kuttner, A. G., and T'ung, T. *Ibid.*, 1935, **62**, 805

St. Louis Encephalitis.

[196] McCordock, H. A., Collier, W., and Gray, S. H. *Journ. Amer. Med. Assoc.*, 1934, **103**, 822.
[197] Muckenfuss, R. S., Armstrong, C., and Webster, L. T. *Ibid.*, 1934, **103**, 731.
[198] Smadel, J. E., and Moore, E. *Amer. Journ. Path.*, 1934, **10**, 827.
[199] Webster, L. T., and Fite, G. L. *Science*, 1933, **78**, 463.
[200] *Idem.* *Journ. Exp. Med.*, 1935, **61**, 103.

Vaccinia.

[201] Douglas, S. R., Smith, W., and Price, L. R. W. *Journ. Path. and Bact.*, 1929, **32**, 99.
[202] Gildemeister, E., and Hilgers, P. *Deut. med. Wchnschr.*, 1930, **56**, 312.
[203] Hurst, E. W., and Fairbrother, R. W. *Journ. Path. and Bact*, 1930, **33**, 463.
[204] Levaditi, C., and Nicolau, S. *Ann. Inst. Past.*, 1923, **37**, 1.
[205] Levaditi, C., Nicolau, S., and Sanchis Bayarri, V. *Presse méd.*, 1927, **35**, 161.
[206] Ohtawara, T. Sci. Rep. Gov. Inst. Infect. Dis., Tokyo, 1922, **1**, 203.
[207] Pette, H., and Kornyey, St. *Zeit. f. Hyg. u. Infektionskr.*, 1933, **115**, 752.
[208] Rivers, T. M., Sprunt, D. H., and Berry, G. P. *Journ. Exp. Med.*, 1933, **58**, 39.
[209] Winkler, W. F. *Arch. f. Hyg.*, 1927, **98**, 241.
[210] *Idem.* *Zeit. f. Immunitatsforsch.*, 1931, **73**, 185.

Virus III.

[211] Miller, C. P., Andrewes, C. H., and Swift, H. F. *Journ. Exp. Med.*, 1924, **40**, 773.
[212] Rivers, T. M., and Stewart, F. W. *Ibid*, 1928, **48**, 603.
[213] Rivers, T. M., and Tillett, W. S. *Ibid.*, 1924, **40**, 281.

Yellow Fever.

[214] Dinger, J. E. *Zent. Bakt.*, Abt. 1, Orig., 1931, **121**, 194.
[215] Findlay, G. M., and Clarke, L. P. *Journ. Path. and Bact.*, 1935, **40**, 55.
[216] *Idem.* *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1935, **28**, 579.
[217] Findlay, G. M., and Stern, R. O. *Journ. Path. and Bact.*, 1935, **40**, 311.
[217·5] *Idem.* *Ibid.*, 1935, **41**, 431.
[218] Goodpasture, E. W. *Amer. Journ. Path.*, 1932, **8**, 137.
[219] Hughes, T. P., and Theiler, M. *Journ. Bact.*, 1934, **27**, 76.
[220] Lloyd, W., and Penna, H. A. *Amer. Journ. Trop. Med.*, 1933, **13**, 1.
[221] Nicolau, S., Kopciowska, L., and Mathis, M. *Ann. Inst. Past.*, 1934, **53**, 455.
[222] Theiler, M. *Ann. Trop. Med.*, 1930, **24**, 249.
[223] *Idem.* *Amer. Journ. Trop. Med.*, 1933, **13**, 399.
[224] Theiler, M., and Hughes, T. P. *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1935, **28**, 481.

THE EFFECTS OF OCCIPITAL LOBECTOMY ON VISION IN CHIMPANZEE.

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INTRODUCTION.

It has long been known that central vision appears to suffer relatively less than peripheral vision following unilateral destruction of the occipital cortex. Indeed, when the striata area is subtotally removed in man, central or macular vision may be more or less completely preserved, the deficit being confined to the peripheral, homonymous fields of the side opposite to the lesion. However, other cases, and they are generally those involving larger lesions, show a complete homonymous hemianopsia of the opposite side including the macular portion of the fields, with the vertical line passing through the points of fixation. For the most part the clinical examination of these cases of injury to the occipital lobe have consisted of field determinations by perimetric methods, and, in a few instances, visual acuity measurements. These latter, however, usually have been made with relatively crude methods and, therefore, have been of little value in interpreting the relation of the visual cortical centres to this function. A further limitation is the fact that the normal visual acuity of the subject, i.e. antedating the pathological condition, is not usually known.

An opportunity to study the effects of occipital lobectomy upon visual acuity in chimpanzee was recently presented to us. The subject of the experiment, a co-operative adolescent female chimpanzee, had been used extensively over a period of two years in a comparative study of human and chimpanzee vision [15], during which stable acuity standards had been established over a medium brightness range. As it was not desired to use this subject for breeding purposes in the Laboratories of Primate Biology it was decided do utilize it in a terminal experiment on the effects of cortical injury upon visual acuity.

Two successive cortical extirpations were made. At the first operation the entire left occipital lobe, including all calcarine cortex, was removed. Visual acuity determinations at four brightness levels were made between the seventh and forty-third day after operation. A second operation involving subtotal extirpation of the right occipital lobe was then performed and visual acuity again tested. An attempt was also made to determine the limits of the fields of vision following each operation. This is the first recorded study of the results of occipital lobectomy in a chimpanzee.

APPARATUS AND METHODS FOR MEASURING VISUAL ACUITY.

Apparatus.—The apparatus employed in measuring visual acuity was the Ives Visual Acuity Test Object[1] [8]. This instrument presents to the subject an illuminated circular field, 7 cm. in diameter, containing black and white striæ equal in width. These striæ, which are produced by the rotation about each other of two glass plates on which are ruled very fine opaque lines, 240 to the inch, may be varied reciprocally as to size and number, increasing in number and decreasing in size as the angle formed by rotating the two sets of grating lines is made larger. When the striæ are very small and viewed at a sufficiently great distance they cannot be resolved by the eye and the test field appears as a circular form of homogenous brightness. Total brightness of the test field remains constant for all sizes of the stimulus bands.

Visual acuity is determined with this instrument by ascertaining the smallest width of stimulus lines that can be resolved by the eye, i.e. that permits the test field being perceived as containing distinct lines and not being of homogeneous brightness. Visual acuity is measured in terms of the angle subtended at the eye by this minimal (threshold) width of the stimulus lines.

A modification of the Yerkes-Watson discrimination apparatus [17] was used in the training. It consisted of an experimental cage, the front wall of which was solid except for two openings, a lower one through which the animal could extend its hands to food boxes and a small upper one (2½ by 4½ in.) at the level of the test objects which provided a window through which the animal could look at them. A single, sliding panel, operated by the experimenter, opened and closed both of these openings simultaneously. The relations of the stimulus objects to the food-boxes is shown in fig. 1. The food-boxes (F_1 F_2), which were contained in a long box (H), were directly below and in front of the two Ives test objects (G_1 G_2), each of which was fastened to the front of a light box. The food box was placed at slightly less than arm's length from the animal's cage. All parts of the apparatus were painted a flat black and were located in a room from which all outside light was excluded. Further details of the apparatus, controls of secondary cues, and measurement of light sources, are described elsewhere [15].

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[1] One of the two instruments used in the present investigation was originally designed and constructed by Dr. H. E. Ives of the Bell Telephone Laboratories as a model for Bausch and Lomb Company. A duplicate of this instrument was made in the shop of the Physics Laboratory of Yale University. The glass gratings were obtained at Max Levy and Company, Philadelphia.

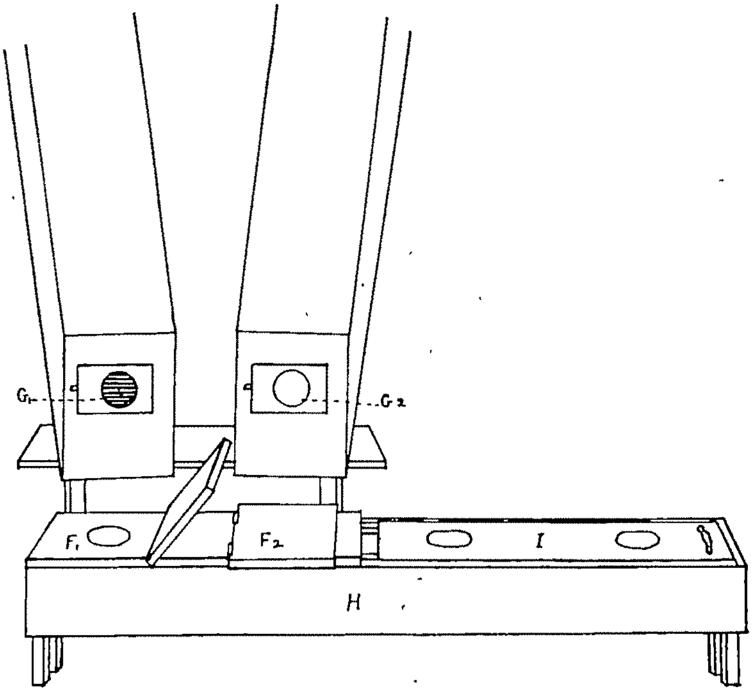

Fig. 1.—Showing the relation of the Stimuli to the Food Boxes. *F*, *F*, Location of food cups; *G*, *G*, Ives visual acuity test objects; *H*, food box; *I*, sliding panel into which food cups fitted.

Experimental procedure.—In the preliminary training the animal was taught that when the sliding panel was raised it was to look through the small window thus exposed and, after observing on which side the circular field containing white and black striae was located, to reach through the lower opening and obtain food from the food box on the corresponding side. If the wrong box was chosen, i.e. the one on the side corresponding to the clear test field, the animal received no reward and was required to withdraw its hand and await another trial, usually given within thirty to forty-five seconds. The positions of the correct and incorrect stimulus fields were varied from left to right according to a chance series with the restriction that the same stimulus was never on one side more than three times in succession.

Once the animal had learned to discriminate so that it was responding without error, i.e. always choosing the stimulus with the lines, determination of thresholds for the perception of the lines was begun. Beginning with stimulus lines that were readily perceived by the animal, the width of the striae was reduced every five trials until the discrimination broke down. The width of the lines was then increased to a value which the animal was well able to discriminate correctly and the procedure repeated until reliable thresholds were obtained. The number of such series of descents varied with the brightnesses and distances of the stimuli.

In the pre-operative tests the animal was used once or twice daily, the number of trials in a given experimental period varying with the degree of motivation. Usually the subject worked from 20 to 35 trials, occasionally as many as 50. A ten-minute period of dark adaptation preceded each experimental series so that when the threshold regions were reached the period of darkness adaptation was at least twenty minutes. The procedure in post-operative tests was essentially the same except that experimentation was limited to one period per day.

SURGICAL PROCEDURES AND POST-OPERATIVE RECOVERY.

First operation (*May* 24, 1933). *Extirpation of the left occipital lobe* (*Area striata*). (*Drs. J. F. Fulton, D. G. Marquis and J. W. Watts.*[1])—Under fairly deep sodium-amytal anæsthesia (20·5 c.c. 10 per cent. solution, injected intra-peritoneally) a large, posteriorly situated, left-sided bone-flap was turned back, the dura opened, and a cellophane tracing and free-hand sketch made of the chief sulci. The extirpation was carried out with the Davis-Bovie electro-surgical unit. After first coagulating the large blood-vessels surrounding the area, the cortex along the occipital sulcus was incised. The remaining part of the dissection was carried out with blunt spatulas, the tissue being removed in a single piece. The extirpated block weighed 18 grm. and included all tissue posterior to the parieto-occipital sulcus and the entire cerebellar surface of the hemisphere up to within about 5 mm. of the corpus callosum; all cortical tissue in the region of the calcarine fissure up to the corpus callosum was then sucked away. Subsequent examination of the brain by Poliak and Rei Hayashi [14] revealed that the excision of the area striata was complete. The dura was reapproximated with silk sutures and the bone-flap replaced in the usual manner.

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[1] The writers wish to acknowledge the assistance of Drs. C. F. Jacobsen, R. U. Light, D. G. Marquis, and J. W. Watts.

Post-operative notes.—Same day: Examination about three hours after completion of operation showed eyes opened and deviated conjugately to the left.

First day: The eyes were deviated to the left but were capable of extreme deviation to the right: The right pupil seemed slightly larger than the left. Gross examination revealed right homonymous hemianopsia.

Second day: The animal moved around her quarters more freely. Although movements were executed slowly there was no indication of motor impairment of the limbs. Eye movements were made with facility in all directions and the pupillary response to light was normal. Detail vision was apparently good, for the animal was able to see and pick up with accuracy small pieces of banana from the floor.

Third day: An examination of the visual fields revealed a right homonymous hemianopsia. When a moving object was passed from right to left in the field of vision, the eyes invariably jumped and were fixated only when the object had reached the mid-line. The conjugate twitching as the object comes into the field of vision was much more marked than is the corresponding phenomenon in a human being. The pupils were approximately equal and eye movements were in all directions. The tendency towards involuntary deviation of the eyes to the left had more or less disappeared. Tests of visual acuity were undertaken after the seventh post-operative day (see below).

Second operation (July 7, 1933). *Subtotal extirpation of the right occipital lobe. (Drs. J. F. Fulton, R. U. Light and D. G. Marquis.)*—Following a procedure similar to that described in the account of the first operation, a partial extirpation of the right occipital lobe was carried out. The block of excised tissue included the entire lateral surface and posterior portion of the lobe, but none of the medial surface overlying the cerebellum. The calcarine fissure was thus left largely intact except for the posterior three or four millimetres. Subsequent examination of the animal's brain showed that the area striata was intact along the anterior three-fourths of the longitudinal extent of the calcarine fissure. Both the area striata and the visual radiation were either absent or damaged in the posterior one-fourth. Fig. 2 shows the site of the excision. A more precise statement of the locus and extent of this injury as observed at autopsy is given by Poliak and Rei Hayashi [14].

Post-operative notes.—Same day: There was little activity throughout the day and no sign of visual perception.

First day: There was no evidence of any visual perception, response to moving objects or menacing gestures being absent. The pupils reacted quite promptly to light, however, and apparently equally well to stimulation from all parts of the visual fields. The eyes were sharply deviated to the right.

Second day: There was no response to a well-illuminated banana in any part of the field of vision. Pupillary reactions appeared less brisk from the left homonymous side than from the right. Conjugate deviation of the eyes to the right was less pronounced.

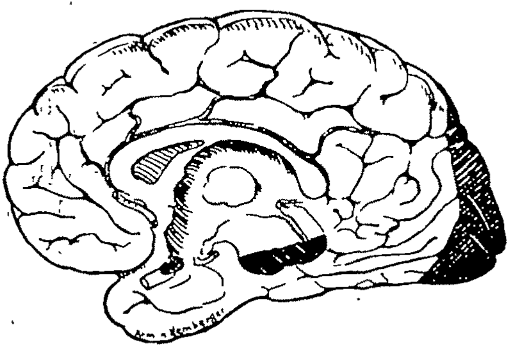

FIG. 2.—Sagittal view of the brain showing the position and extent of the lesion as seen at the second operation.

Third day: The animal moved around in her quarters more freely, but her actions were like those of a blind person. There was no visual response other than the pupillary reflex.

Fifth day: Flashing an ophthalmoscope into various parts of the visual field gave one the impression that the subject possibly had some awareness of light in the peripheral part of the left homonymous field. There was a complete lack of response to the flashing of the light in the right homonymous field. When allowed to go into the cage outside of the living room for the first time the animal went groping about the cage, bumping into various objects such as posts and suspended automobile tyres. There was nothing in the behaviour of the animal to suggest any useful vision whatever

Eighth day: When examined in the brilliant daylight of the outside cage the animal showed unequivocal response to objects moved and held in the left homonymous visual field. After having eaten several pieces of banana she would reach with surprising accuracy for a piece of banana moved in the left field at distances as great as two feet from the eyes. There was no comparable response when the banana was moved about in the right field. In moving about the cage the animal still seemed to feel its way about rather than to depend upon optical impressions. There was no blinking response to threatening gesture made towards the eyes.

Eleventh day: Occasionally, during the last two or three days, S. seemed to follow pieces of food moving in her left visual field. To-day a more adequate test was made in which the food was moved across the right and left visual fields in random order. Five trials were given on each side. S. responded by reaching for the food each time it was presented in the left visual field and not once in the right field. During the test no word was spoken or noise made that might have provided it with a cue. The blinking response continued to be absent.

Fourteenth day: The blinking response to gestures made towards the eyes was observed for the first time.

Fifteenth day: The animal blinked and cowered when a pretence of striking her was made at a distance of five feet. There was no possibility of responding on the basis of auditory stimuli to these threats as there were steady masking noises.

Sixty-eighth day: Observations by Dr. D. G. Marquis at intervals throughout the period since operation show a progressive increase in visual ability. The animal now responds promptly to food held before it, reaching out with either arm and grasping it accurately. The blinking response to menacing gestures is very definite in the left field, but entirely absent in the right. Objects moved slowly back and forth in front of the eyes are followed with jerky movements, but not with smooth pursuit movements. The animal is now able to move about the cage in apparent normal fashion, climbing on the window ledge and swinging from the roof. It never strikes or bumps into objects even on its blind field.

Seventy-third day: Examination by Dr. M. A. Kennard showed no vision in the right field, and furthermore that this blind region extended somewhat to the left of the mid-line. Left peripheral vision was described as surprisingly keen and accurate.

ACUITY MEASUREMENTS.

The rough threshold determination employing the psychophysical method of limits, in which the size of the stimulus lines is reduced on each succeeding trial until the animal fails, was made three days before the first operation to insure the intactness of the discrimination habit. The value of 0·84 minutes for the test objects at a brightness of 3·98 millilamberts and at a distance of 75 cm. was almost identical with that of 0·85 minutes obtained in the previous extended series of observations [15].

On the sixth day after the *first operation*, S. was given five trials with stimulus lines that were well above threshold. S. responded readily and accurately on each occasion, looking from one stimulus to the other before making her choice. It was observed that the head was invariably turned to the right when looking at the test objects immediately in front of her. There seemed to be little, if any, disturbance of the discrimination habit.

On the ninth day a rough determination of the visual acuity employing the method of limits was made. The value obtained was 0·995 minutes as compared to 0·84 minutes obtained by the same procedure in the retention test given just prior to operation. After this experimental period S. failed to work satisfactorily for almost three weeks, usually responding only two or three times on each occasion. Apparently food motivation was low since S. often opened the food box, took the food and, after examining it, dropped it on the floor. During this time S. was nervous and irritable, and it is possibly of some significance that the genital swelling increased throughout this period and reached the maximum on June 20, the day before S. again worked systematically.

From June 22 to July 6 S. worked excellently and her behaviour compared favourably with that of the pre-operative work. One difference that did stand out, however, was that S. no longer became angry or flew into temper tantrums upon a series of successive failures as had occurred in the pre-operative tests. This difference was apparently not related to lessened motivation as S. worked eagerly for the lure, large cherries, of which she was especially fond.

Visual acuity measurements were made at a distance of 75 cm. in the regular manner at four brightness values of the test-objects, 14·06, 3·98, 0·986, and 0·0176 millilamberts. In Tables 1A and 1B pre-operative and post-operative data are presented showing the percentage of correct responses and the total number of trials given at each size of the stimulus lines for these several brightnesses. It is apparent that the ranges of the critical stimulus values of the post-operative period, i.e. the points at which the animal responded with an accuracy less than 100 per cent., overlap those of the pre-operative period. At each brightness, however, the accuracy of response decreased more quickly in the post-operative tests than in the pre-operative. The threshold values, taken as the size of the stimulus line at which the animal responded correctly 75 per cent. of the trials, are given in Table II. Inspection shows that the thresholds were slightly, but nevertheless consistently, higher (poorer) at all brightness, in the post-operative tests, visual acuity being between 85 and 95 per cent. of pre-operative vision.

Whether this slight loss represents a genuine loss in visual capacity or whether it is due to other factors is not clear. The behaviour of the animal in the experimental situation after the operation gave no indication that the slightly poorer performance resulted from lessened motivation or attentiveness. Once S. started responding systematically, she worked as willingly and carefully as she had pre-operatively. The one change in behaviour, the absence of rage and temper tantrums after repeated failures, was, if anything, more favourable to careful work since such emotional outbursts were often followed by a series of careless, random responses. This qualitative evidence is further supported by the fact that the average time of response was about the same for both periods, the time increasing to about the same point as the threshold (75 per cent. accuracy) was approached, and decreasing slightly thereafter as more and more random responses were made with the inability to discriminate.

The available evidence suggests, then, that the poorer measures do indicate a genuine but slight loss in efficiency of the visual system. This conclusion is further strengthened by the fact that at 3·98 millilamberts three independent measures of visual acuity, obtained by different psychophysical procedures [15], gave highly consistent measures of 0·81, 0·84 and 0·85 minutes while two post-operative measures gave 0·98 minutes and 0·995 minutes. The loss is slight, however, and by no means proportional to the amount of the visual system that was destroyed.

No attempt was made to test S.'s visual acuity until the sixteenth day after the *second operation* as there was little evidence before this of visual function other than that of light or movement perception. She refused to work on this occasion and took food only when it was given through the small opening of the apparatus. Even with the room lights on she groped around in blind fashion.

S. remained unco-operative for several days, even refusing to go into the experimental cage. On the twenty-first day, however, she worked for twenty trials. The test fields were at a brightness of 3·98 millilamberts and the stimulus lines in the positive field were fairly large, subtending a visual angle of 13·8 minutes at a distance of 75 cm. In twenty trials the animal responded correctly only nine times, indicating that she was quite unable to discriminate lines of this size. Her behaviour, however, suggested that she could at least differentiate between the two circular stimulus fields, for in the early trials she appeared to look back and forth from one test field to the other before making a choice. In the latter part of the period she became restless and usually responded immediately after the sliding door was raised

TABLE IA.—SHOWING THE PERCENTAGE OF CORRECT RESPONSES AND THE TOTAL NUMBER OF TRIALS GIVEN AT EACH SIZE OF THE STIMULUS LINES.

Visual angle in minutes	Brightness of test objects (millilamberts)							
	0·176				·986			
	Pre-operative		Post-operative		Pre-operative		Post-operative	
	Per cent. correct	Number of trials	Per cent. correct	Number of trials	Per cent. correct	Number of trials	Per cent. correct	Number of trials
2·141			100·0	20				
1·985	100·0	40	95·0	20				
1·871	90 0	80	90 0	20				
1·737	86 3	80	80·0	15				
1·636	88·8	80	80 0	15				
1·542	75·0	80	53·0	15				
1·464	70·0	70						
1·392	62·5	40						
1·325	58·3	80						
1·265							100·0	15
1·211							95·0	20
1·160							80·0	20
1·114					100·0	80	75·0	20
1·070					96 7	30	80·0	20
1·030					91·7	60	60·0	25
0·995					91·7	60		
0 961					83·3	60		
0·929					81·0	60		
0 899					67·5	80		
0·871					68·3	60		
0·845					50·0	20		

without looking in the direction of either stimulus object. However, in neither half of the period did S. make a significantly greater number of correct responses than might be expected by chance, i.e. one-half.

TABLE IB.—SHOWING THE CORRECT RESPONSES AND THE TOTAL NUMBER OF TRIALS GIVEN AT EACH SIZE OF THE STIMULUS LINES.

Visual angle in minutes	Brightness of test objects (millilamberts)							
	3·98				14·06			
	Pre-operative		Post-operative		Pre-operative		Post-operative	
	Per cent. correct	Number of trials	Per cent. correct	Number of trials	Per cent. correct	Number of trials	Per cent. correct	Number of trials
1·160			100·0	20				
1·114			95·0	20				
1·070			84·0	25				
1·030	100·0	20	80 0	25				
·995	100·0	20	84·0	25	100·0	20		
·961	93·3	60	60 0	25	100·0	30		
·929	93·0	70	59 0	10	96·7	60	100.0	10
·899	81·4	70			93·3	60	90 0	10
·871	81·4	70			91·6	60	80·0	10
·845	75·0	60			90·0	60	50 0	10
·820	70·0	60			80 0	60		
·797	62·0	50			86 7	60		
·775	55·0	20			73·3	60		
·754					71·0	80		
·735					56·7	60		
·716					50·0	10		

TABLE II.—SHOWING THRESHOLDS (VISUAL ANGLE IN MINUTES) FOR THE PRE-OPERATIVE AND POST-OPERATIVE PERIODS.

Experimental period	Brightness of test objects (millilamberts)			
	14 06	3 98	986	0176
Pre-operative	·78	·85	·92	1·54
Post-operative	·87	·98	1·07	1·62
Pre-operative / Post-operative	·896	·867	·86	·95

VISUAL FIELD DETERMINATIONS.

Determination of visual field defects in animals is a most difficult matter. Attempts were made, however, to discover the effects of the operations upon the limits of the visual fields by the method of presenting to the animal in a more or less systematic fashion moving pieces of food or other objects in various portions of its visual fields and observing the responses of the eyes and the attempts of the animal to obtain the food. The crudity of these methods requires, of course, that the observations be accepted and interpreted with considerable caution.

The results of these studies suggest that after unilateral destruction of the left striate area there was a right homonymous hemianopsia. That this loss in the right fields was complete, including at least a part of a macular vision, is suggested by the post-operative note of the third day to the effect that the eyes fixated only when the object had reached the mid-line. This conclusion receives added support from the observation that the animal always turned its head well to the right when looking at the test objects.

The second operation further delimited the fields of vision so that only the extreme left peripheral regions, probably corresponding to the temporal half-moon [9], remained functional. That there was in all probability a central scotoma is suggested by the following observations: (1) When objects were moved from the right field to the left no response was made until the object reached a point some distance to the left of the mid-line; (2) the animal never picked up objects directly in front of it but always turned its head to the side. The very low visual acuity test results, i.e. failure to discriminate a pattern of lines subtending an angle as large as 13·8 minutes, also support this conclusion.

DISCUSSION AND INTERPRETATION OF RESULTS.

The relation of visual acuity to the neurological elements, both peripheral and central, is a complex one, about which comparatively little is known. However, the studies of Hecht and others [3, 4, 5, 6] have presented fairly clear-cut evidence suggesting that visual acuity is a function of the density or grain of the elements, rods and cones, in the retina. The most important fact in support of this conclusion is that visual acuity varies in different parts of the retina according to the density of the elements, being greatest in the macular area where there are the greatest number of elements per unit area and least in the peripheral regions in which the independent elements are less dense.

It will readily be seen, then, that the effect on visual acuity to be expected from the removal or destruction of any part of the visual cortical elements will depend upon the nature of the relation of these structures to those of the retina. The effects on the fields of vision resulting from partial and complete unilateral occipital lobectomies have led to one conception of this relationship as involving a strict anatomical point-to-point projection of the retina upon the visual cortex. This view very successfully accounts for the cases of small circumscribed scotoma resulting from limited lesions and for the various quadrantic and hemianoptic defects resulting from larger partial and complete unilateral lesions.

Objections have been raised, however, to this conception of a specific, fixed relationship, particularly in the case of macular vision. The critics, while willing to recognize some degree of specific localization, deny that this organization is anything more than a crude one. The strict localistic principle does not hold, they claim, for the finer internal organization of the macular area. These objections are based upon various observations, one of the most important of which is the preservation of central vision (macular sparing) that sometimes occurs in cases of supposed, complete unilateral damage to the visual cortex. Such cases, if really involving a complete unilateral ablation, are truly embarrassing for this point of view. They are, on the other hand, nicely explained on the basis of a diffuse organization of the macula such that the fibres from the various parts of each macula are distributed in a random manner to both visual cortical areas. The ablation of one of these areas would result in no particular portion or area of the maculæ becoming functionless but only in a reduction in the density or number of the elements throughout each total macula.

The implication of this latter view for visual acuity measurements is obvious. With the reduction in the density of the functional elements, which would presumably be decreased about half, as this proportion of the macular fibres are estimated to cross in the chiasma, a corresponding loss in visual acuity would be expected. This expectation was not realized in the present investigation. Further evidence contradicting such a view is the fact that there is no macular sparing in cases in which the optic tract itself is completely interrupted, thus showing that fibres from the temporal halves of the maculæ do not cross over to the opposite hemisphere, at least not by way of the optic chiasma.

A somewhat different hypothesis that has been put forward to explain these cases of macular sparing is that a portion of the visual radiation crosses to the striate area of the opposite hemisphere through the splenium of the corpus callosum [1, 2, 7, 10, 11, 12, 16]. The results of the present experiment are not conclusive as regards this hypothesis, as the effect on visual acuity of a unilateral occipital lobectomy to be expected on the basis of it would depend on several things. First of all, it would be a function of the proportion of the macular fibres that cross in the corpus callosum, and it also would depend upon whether the decussating fibres provide dual cortical representation, i.e. by a branching of the individual fibres from the macular elements, one branch decussating to the opposite hemisphere and the other continuing to the ipsilateral one, or whether there was simply a single cortical element corresponding to each macular element.

If we assume that the proportion of decussating fibres is about half and that it is roughly an alternate fibre affair, the effect of complete destruction of the left occipital cortex would be as follows: (1) With the further assumption that the decussating fibres provide dual cortical representation, the density of the grain in the ipsilateral homonymous hemi-maculæ would be decreased by half with an approximately corresponding decrease in visual acuity. However, the density of the elements in the contralateral or right halves of each maculæ would not be decreased and consequently visual acuity measurements would not be expected to show any decrease unless confined to the left hemimaculæ. (2) On the assumption that the crossed fibres do not provide double cortical representation, i.e. that there is no branching of the macular fibres, the density of the grain in both halves of each maculæ would be decreased by half and one would thus expect a corresponding decrease in visual acuity. The results of the present experiment are not in harmony with the latter variation of the hypothesis. To determine the validity of the former, determination of visual acuity for different regions of the maculæ is needed. Such a study would require the co-operation that only human subjects can provide.

The purpose of the second operation was to determine whether the macula of the chimpanzee, as Poliak has demonstrated for the monkey [13], is projected on the posterior portion of the striate area in the region of the occipital pole. In this operation the posterior one-fourth, including the entire lateral surface of the right occipital lobe, was either damaged or removed. There was thus a complete bilateral removal of the supposed macular cortical areas. In such a subject central vision should be non-existent.

The experimental tests of visual acuity and observations of field defects tended to confirm this expectation. Visual acuity was considerably below that to be expected of the macular region for even the lowest illuminations, while the visual field tests indicated that vision was present only in the extreme peripheral portion of the left field. This latter observation is also in agreement with the numerous studies of men, which show that the far periphery of the visual field [9], the temporal half-moon or crescent as it is sometimes termed, is projected on the anterior part of the area striata along the calcarine fissure, the only portion of the lobe left intact by the operation.

SUMMARY AND CONCLUSIONS.

This investigation is concerned with the relation of the visual cortical areas to visual acuity. An adolescent chimpanzee whose visual acuity had been carefully determined by the Ives visual acuity test object over an intermediate range of brightness levels was subjected to the following operations: (1) Complete extirpation of the left occipital lobe; and (2) extirpation of the posterior and lateral portions of the area striata of the right hemisphere.

Subsequent to each operation visual acuity measurements were made with the following results:—

(1) The removal of the entire left area striata resulted in a slight, but consistent loss in visual acuity ranging from approximately 5 to 15 per cent. at four brightness levels.

(2) Following the second operation, which left the animal with only the anterior portion of the right area striata intact, there was complete failure to discriminate a pattern sixteen times as large as that discriminated in the pre-operative tests.

Rough testing of the visual fields suggested that a right homonymous hemianopia resulted from the first operation, while the second spared only the extreme left peripheral fields, i.e. the temporal half-moon. This latter result supports the view that the occipital pole of the area striata represents the macular projection area and the anterior portion of the area striata around the calcarine fissure is the cortical terminus of the extreme peripheral retinal elements.

REFERENCES.

[1] FOERSTER, O. "Beiträge zur Pathophysiologie der Sehbahn und der Sehsphäre," *Journ. f. Psychol. u. Neurol.*, 1929, **39**, 463-485.

[2] FOERSTER, O., and PENFIELD, W. "Der Narbenzug am und im Gehirn bei traumatischer Epilepsie in seiner Bedeutung fur das Zustandekommen der Anfalle und fur die therapeutische Bekampfung derselben," *Zeitschr. f. d. ges. Neurol u. Psychiat.*, 1930, **125**, 475-572.

[3] HECHT, S. "The Relation between Visual Acuity and Illumination," *Journ. Gen. Physiol.*, 1928, **11**, 255-282.

[4] *Idem.* "The Nature of the Photoreceptor Process. Foundations of Experimental Psychology." Worcester, Mass.: Clark Univ. Press, 1929, pp. x + 907.

[5] HECHT, S., and WALD, G. "The Influence of Intensity on the Visual Functions of Drosophila," *Proc. Nat. Acad. Sciences*, 1933, **19**, 964-972.

[6] HECHT, S., and WOLF, E. "The Visual Acuity of the Honey Bee," *Journ. Gen. Phys.*, 1929, **12**, 727-760.

[7] HENSCHEN, S. E. "Sur les localisations dans le ganglion genicule extreme," *Rev. Neurol.*, 1897, **5**, 619-620.

[8] IVES, H. E. "A Visual Acuity Test Object," *Electrical World*, 1910, **55**, 939-940.

[9] KRONFIELD, P. C. "The Temporal Half-moon," *Trans. Amer. Ophthal. Soc.*, 1932.

[10] LENZ, G. "Zur Pathologie der zentralen Sehbahn unter besonderer Beruecksichtigung iherer Ergebnisse fur die Anatomie und Physiologie," *Arch. f. Ophthal.*, 1909, **72**, 1 and 187.

[11] PENFIELD, W., and EVANS, J. "Functional Defects Produced by Cerebral Lobectomies," *Proc. Assoc. Research Nerv. and Ment. Dis.*, 1932, **13**, 352-378.

[12] PENFIELD, W., EVANS, J., and MACMILLAN, J. A. "Visual Pathways in Man, with Particular Reference to Macular Representation," *Arch. Neur. and Psychiat.*, 1935, **33**, 816-834.

[13] POLIAK, S. "The Main Afferent Fiber Systems of the Cerebral Cortex in Primates." Berkeley, Cal.: Univ. Cal. Press, 1932, **2**, xiv + 370.

[14] POLIAK, S., and HAYASHI, REI. "The Cerebral Representation of the Retina in the Chimpanzee," *Brain*, this issue.

[15] SPENCE, K. W. "Visual Acuity and Its Relation to Brightness in Chimpanzee and Man, *Journ. Comp. Psychol.*, 1934, **18**, 333-361.

[16] WILBRAND, H., and SAENGER, A. "Handbuch der Neurologie des Auges." Weisbaden: J. F. Bergmann, 1917, **7**.

[17] YERKES, R. M., and WATSON, J. B. "Methods of Studying Vision in Animals," *Behav. Monog.*, 1911, **1**, No. 2.

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THE CEREBRAL REPRESENTATION OF THE RETINA IN THE CHIMPANZEE.[1]

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THE great strides made during the past twenty years in revealing the internal organization of the afferent visual pathway in man and other primates are chiefly due to careful experimental and pathologico-anatomical investigations. It has been said that the anatomical study of the brain in cases of disturbance of the visual fields has lagged behind the clinical analysis, but this defect has been remedied in recent years by the work of Holmes [4, 5], Brouwer [1, 2], Pfeifer [8], and others, in which the central portions of the visual pathway, the optic radiations and the striate area (field 17) have been examined.

This work, together with the investigations of Rönne [14], of Brouwer and Zeeman [3], of Juba [6], and of Le Gros Clark and Penman [7] on the composition of the peripheral parts of the visual pathway from the retina to the lateral geniculate bodies, and with the studies of the central portion of the visual pathway from the lateral geniculate bodies to the striate area of the cerebral cortex undertaken by one of the present writers [Poljak, 9, 10, 11, 12, 13], and by other investigators in recent years, have helped to provide a fairly detailed conception of the internal structure of the entire afferent visual system; that is, of the position of the different quadrants and in particular of the macula in the optic nerve and tract, in the lateral geniculate body and in the striate area.

The result of all these investigations may be briefly stated as follows: The optic nerve-fibres originating in the retinal periphery corresponding with the upper and lower quadrants of the retina terminate in the medial and lateral segments of the lateral geniculate bodies respectively. The optic nerve-fibres originating in the macula terminate in the large intermediate segments of the lateral geniculate bodies. The most dorsal and the most ventral bundles of the visual radiation originate

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[1] This work was undertaken with the help of grants from the Douglas Smith Foundation and from the Josiah Macey Junior Foundation.

in the medial and lateral segments of the lateral geniculate body respectively, terminate in the upper and lower lip of the calcarine fissure, and correspond with the upper and lower extramacular quadrants of the retinæ respectively. The intermediate bundle of the visual radiation originates in the large intermediate segment of the lateral geniculate body, is placed between the "peripheral" bundles (has an "axial" position in the radiation), is the longest of all and terminates in the posterior portion of the striate area around the tip of the occipital lobe. This bundle and its terminal cortex correspond with the homonymous halves of both maculæ.

As is well known, in the attempts to determine the inner composition of the afferent visual system, experiments on monkeys have played a conspicuous role. For this reason it was considered of some value to report the following case of a chimpanzee operated upon and observed during a period of more than five months by Professor J. Fulton, of Yale University, who kindly sent its brain to one of us. (This animal, under the name of "Kani," female, weighing 35 kg., came from Professor Yerke's division of the Yale University where it was used for the study of visual acuity.)[1]

The following is a brief extract from a protocol of Professor Fulton on the operations performed and on the behaviour of the ape:—

> *In the first operation a radical extirpation of the entire left occipital lobe, including all of the calcarine cortex,* was made. On the next day the eyes deviated to the left, but were capable of extreme deviation to the right also. This tendency to deviate disappeared during the next few days. The right pupil was slightly larger, but this difference disappeared on subsequent days. The palpebral fissures were equal. There was no nystagmus. On the second post-operative day, upon gross examination, there was an obvious and apparently complete right homonymous hemianopsia which seemed to disturb the visual behaviour of the animal very little. On the third day no vision in the right homonymous halves could be detected, the deficit reaching exactly to the vertical meridians. This complete right-sided hemianopic blindness remained without change until the death of the animal five months and five days later (reckoned from the date of the first operation).
>
> Forty-four days after the first *the second operation* was undertaken : *sub-total removal of the right occipital lobe.* The purpose of the second experiment was *to remove the region of the occipital lobe which in man and monkey contains the macular representation,* viz. the lateral surface of the occipital lobe, leaving intact the portion of the calcarine fissure coursing along the medial surface of

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[1] The results of the physiological examination of the same case are being published in a separate paper in this journal by Prof. Fulton and Dr. Spence. After having read the manuscript we are glad to acknowledge our satisfaction with the high degree of accuracy of their work.

the hemisphere. On the first post-operative day, when the animal was at rest, there was a tendency toward the deviation of the eyes to the right with a very marked nystagmus with slow component to the right, and occasional vertical nystagmus. The various tests applied revealed no sign of visual perception of moving objects, or of strong light. No blink-reflex or response to any sort of visual stimuli was noticeable, and whenever touched the animal was evidently surprised, as would be a normal animal in darkness. On the fifth day, flashing an ophthalmoscope into various parts of the visual fields gave the impression of a possible awareness of light in the peripheral parts of the left homonymous fields, although this was not yet certain. On the eighth day the animal showed an unequivocal response to objects moved and held in the left homonymous visual fields. After she had eaten one or two pieces of banana she reached for a banana held or moved in the left fields at distances as great as two feet. There was no comparative response in the right homonymous fields. Her accuracy in localizing the objects was surprising, often coming within inches and striking the observer's wrist, for example. There was no blinking response to threatening gestures made toward the eyes. In moving about the cage she seemed to feel her way rather than to depend upon visual impressions, but when excited she chased the observer and seemed to be able to localize him when there were no obvious auditory cues. Fourteen days after the second operation, for the first time, it was possible to observe the winking response to gestures made toward the eyes. There was an unmistakable response to movements in the left homonymous visual fields, but not to movements in the right fields. No difference between the superior and inferior fields (quadrants) could be detected. This situation remained the same in all particulars during almost five months after the second operation. Even on the day that the animal was sacrificed it still responded only to visual stimuli falling in the periphery of the left homonymous fields, without evidence of a useful central (foveal, macular) vision. Otherwise, during the observation, no pathological signs other than the visual defects were noticed.

The histological examination of the serial sections stained with thionine blue, made by the authors, revealed the following pathological changes :—

In *the left cerebral hemisphere* there was a complete absence of the striate area of Elliot Smith, i.e., the field 17 of Brodmann. As a consequence of this it was found that the nerve-cells of the left lateral geniculate body were completely degenerated, no trace of normal cells being left in any part of the nucleus. There was also marked partial degeneration in the pulvinar of the left thalamus due to the partial injury of the area peri-para-striata or fields 18-19. The left corpus or griseum prægeniculatum was found to be normal. Because of the above findings the left hemisphere will not be further considered in the following.

The *right cerebral hemisphere* showed a more restricted lesion limited chiefly to the tip or pole of the occipital lobe (stippled areas in fig. 1. The narrow crudely shaded area indicates the normal striate area hidden in the calcarine fissure). The cross-sections through the right occipital lobe (fig. 2) revealed a complete absence of that portion of the striate area which in the chimpanzee normally spreads over the occipital pole to its lateral surface along the external calcarine sulcus (the exact limits of the lesion in the drawing A, in fig. 2, are not given, but merely the outlines of the actual section; the approximate extent of the removed substance can easily be noted). A limb of the lesion (stippled) penetrates into the substance of the lobe from below and interrupts a considerable portion of the lower or ventral bundles of the visual radiation (vr). A similar destruction of a portion of the cortex coating the upper lip of the calcarine fissure (fc) can be considered as its counterpart. (In the drawing A this portion of the destroyed cortex is missing, in the drawing B a small triangular lesion partly undermines the cortex in the upper lip.) The last vestiges of the two mentioned lesions—the one in the upper portion of the visual radiation, and the other in the lower portion of the radiation—are still visible in

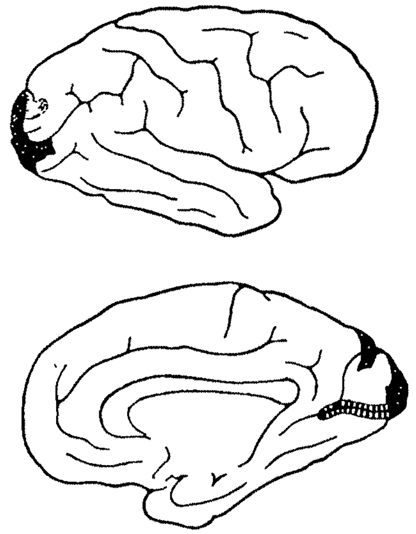

FIG. 1.—Right cerebral hemisphere of a chimpanzee showing in the upper figure a lateral view, in the lower figure a medial view. Damaged portion of the occipital lobe still present is indicated by stippling, the longitudinal extent of the normal striate cortex is indicated by coarse shading. The striate area in reality does not appear on the surface of the brain but is hidden in the calcarine fissure. (Compare crudely shaded portions of the cortex in fig. 2.)

the drawing C, in fig. 2, but anteriorly, in the drawing D of the same figure, only the normal cortex and the normal visual radiation were present. Possibly, the vertical or macular branch of the radiation was somewhat atrophic; this, however, was difficult to evaluate owing to the method of staining applied (thionine-blue). The approximate extent of the normal striate cortex as seen when projected upon the inner face of the hemisphere is represented by a narrow, vertically-shaded area in the lower drawing in fig. 1, stretching along the

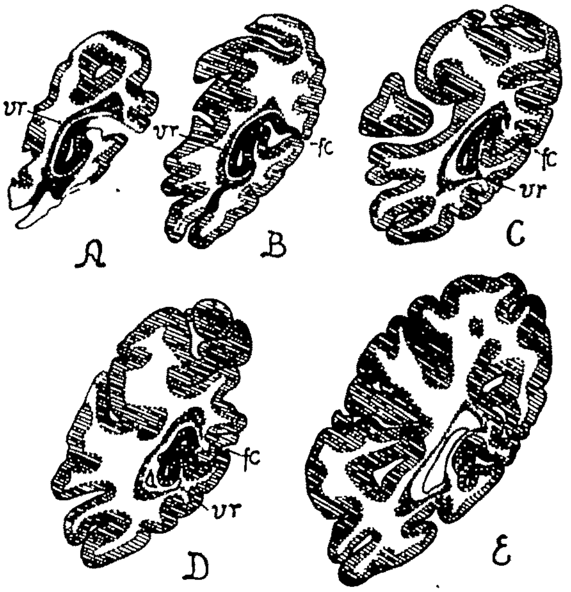

FIG. 2.—Transverse sections through the right occipital lobe depicted in fig. 1. The caudal end of the lobe in the drawing A. The normal portions of the striate cortex crudely shaded, the non-striate cortex lightly shaded, the lesion stippled; fc = calcarine fissure; vr = visual radiation.

calcarine fissure. In order to evaluate the extent of the damage to the visual pathway and to the visual projection cortex it is necessary to consider that the cortex in the depth of the calcarine fissure along its greater anterior and middle longitudinal extent does not receive its afferent visual or any other fibres directly, that is, from the segment of the visual radiation apparently nearest to it (which would be the vertical branch of the radiation, thus in the drawings B, C, D, in fig. 2), since this vertical portion of the radiation is separated from the calcarine cortex by the lateral ventricle (visible only in the drawings D and E, in fig. 2), or by its vestige, thus forcing the incoming or outgoing fibres to turn around the ventricle either from below or from above in order to reach or to leave the "calcar avis." (Exceptions are the "axial" or macular bundles that pass straight to the tip of the occipital pole, the same that in the aggregate form the vertical branch of the radiation.) Since in our case there was some damage done to just the two-mentioned localities, as illustrated by the two small lesions in the upper and in the lower segments of the visual radiation (in the drawings B and C, in fig. 2) the amount of the striate cortex deprived of afferent fibres is somewhat larger than the striate cortex actually destroyed. It is also to be considered that the subcortical, direct damage to the lower segment of the radiation in the lower lip of the calcarine is somewhat more extensive than that to the upper segment in the upper lip of the calcarine fissure. In any event it can be said that in our case the anterior portion of the striate area and its afferent fibres of the visual radiation remained wholely intact.

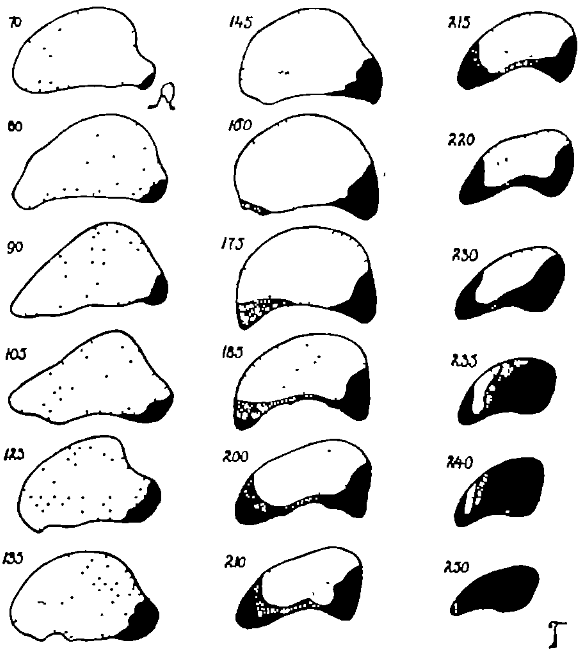

FIG. 3.—Serial sections at fairly regular intervals through the entire lateral geniculate body of the right side, ipsilateral with the lesion. The caudal end of the nucleus is at the drawing A, its rostral beginning at the drawing T. The left sides of the individual drawings are the inner or medial, the right sides of the drawings are the outer or lateral. The normal portions of the nucleus are in solid black, the completely degenerated are lightly stippled, the atrophic ones are densely stippled.

The extent of the complete retrograde degeneration (fig. 3, thinly stippled areas) or of the atrophy of the nerve-cells (densely stippled areas) in *the right lateral geniculate body*—the consequence of the cortical injury to the afferent nerve-fibres taking origin from the nerve-cells of the mentioned nucleus—is illustrated in fig. 3 (normal portions black; the accompanying numbers indicate the sections). The first that one notices is that in the sections closer to the caudal end of the lateral geniculate body (this end is at A) the degeneration is more complete, extending almost over the entire nucleus, not sparing even the large cells of the ventral layers. Only the tip of its lateral segment preserved a nest of approximately normal large nerve-cells. As one proceeds toward the middle of the longitudinal extent of the nucleus (middle column in fig. 3), the degeneration, while still occupying the bulk of the nucleus, becomes gradually narrowed by the increasing medial and lateral zones where the cells appear normal or only more or less atrophic. These normal zones occupy chiefly the two outward segments, the innermost or the medial, and the outermost of the lateral (left and right, respectively, in the individual drawings, in fig. 3), both zones or segments being barely connected with one another by means of a narrow zone spreading along the lower or ventral contour of the nucleus. In sections corresponding with the anterior or rostral one-third of the geniculate body (right column in fig. 3) this more or less normally appearing strip increases somewhat in thickness, although even in the most anterior sections of the nucleus (close to T in the right column, fig. 3) a narrow strip that touches the ventral contour remains where the nerve-cells do not appear quite normal. On the other hand, in the oral one-third of the nucleus the relative sizes of the normal segments increases until near its anterior end almost the entire nucleus appears to contain normal nerve-cells.

In trying to correlate the size and location of the lesion in the right occipital lobe with the size and location of the retrograde cell-degeneration of the lateral geniculate body of the right side we are at some disadvantage because the exact projection of the various peripheral and macular quadrants of the retina upon the lateral geniculate body in the chimpanzee is not known. Yet we think that a certain comparison with the geniculate projection in man and in lower monkeys known from the investigations of Rönne, Juba, Brouwer-Zeeman and Le Gros Clark-Penman is permissible, at least as an approximation. From this we conclude that in the champanzee, too, the macular portions of both retinæ are projected upon the large intermediate segment placed more toward the caudal end of the lateral geniculate, while the upper and lower extramacular quadrants are represented in the medial and lateral segment, of the same nucleus respectively. If this be correct—as it is very likely—then the portion of the lateral geniculate nucleus degenerated in our case corresponds chiefly with the hemimaculæ, the portions remaining normal correspond with the extramacular portions of the homonymous hemiretinæ including the monocular crescent. This in turn leads to the conclusion that the anterior portion of the striate area which lines the posterior and larger portion of the calcarine fissure—which in our ape remained largely intact (crudely shaded narrow area in fig. 1)—corresponds also with the extramacular portions of the retinæ, or of the visual fields respectively, whereas the portion of the striate area covering the tip of the occipital lobe and spreading over its postero-lateral face, removed in our case, is the portion where the hemimaculæ, respectively the centres of the visual fields, are represented.

This all fits very well with the character of the observed defect of the fields of vision, where the central portions were absent on the left side during the life of the animal, which extended over almost five months after the second operation. This, too, is in perfect accord with those numerous observations of the human cases which have led to the conviction that the macular representation is near the tip of the occipital lobe, in the caudal portion of the striate area. True, the absence of an exact perimetric study of the functional loss in our case, and the fact that the extent of the macular territory in the lateral geniculate body is not known in the apes and was here merely conjectured from the analogy with the human conditions [Rönne, Juba] permits only an approximation. Nevertheless, our case shows that the assumption made earlier and again in recent times, viz., that the macula may partly be represented in the anterior portion of the striate area, or that the macula is diffusely represented, is ill-founded. The large size of the degenerated segment of the lateral geniculate body, ample enough for the entire macula, even if its size is generously measured, tells against the above assumption. (In fact, we suspect that considerably more than the macular cortex proper was eliminated in our experiment.) At least it appears that the anterior portion of the striate area, which in our case remained intact, is in no way directly connected with central or macular vision. On the other hand, for the problem of quadrantic representation there is little of value in the present case. Perhaps the smaller size of the inner or medial segment of the lateral geniculate body that remained normal (left ends of the drawings in fig. 3) in comparison with the lateral segments (right ends of the drawings in fig. 3) is due to the larger lesion that interrupts the upper portion of the visual radiation and the upper lip of the calcarine fissure (thus in the drawings A, B in fig. 2) if compared with the smaller lesion damaging the lower lip of the calcarine fissure (small stippled areas in B and C, in fig. 2). This, too, would conform to the generally accepted schema according to which the upper quadrants of the retinæ (lower quadrants of the visual fields) are represented in the upper lip of the calcarine fissure and in the upper or dorsal bundles of the visual radiation; the lower quadrants of the retinæ (upper quadrants of the visual fields), on the contrary, in the lower lip of the calcarine fissure and in the lower bundles of the radiation.

Finally, the completeness of the degeneration of the nerve-cells in the intermediate segment of the lateral geniculate nucleus does away with the assumption that any number of the nerve-cells composing the lateral geniculate nucleus may be the so-called intercalated or associational elements, cells with a short axis cylinder of the Golgi type II. The same fact is also inconsistent with the view that some of the geniculate cells, especially the large ones, may send their axis cylinders to the superior colliculi or elsewhere and not to the cortex. It is more plausible that, since all geniculate cells—including the large ones in the ventral layers of the nucleus—completely disappear in consequence of the lesion to the occipital lobe, all of them give rise to axis cylinders which terminate in the striate area.

The fact that the circumscribed lesion of the caudal end of the striate area produces a sharply delimited degeneration in the intermediate or macular segment of the lateral geniculate body once more disproves Monakow's concept still adhered to by some, viz., that the macular fibres of the visual radiation spread over the entire territory of the striate area. Our case shows that the macular fibres have a well delimited area in the cerebral cortex, the posterior portion of the striate area, beyond which they do not reach. This concept is based chiefly upon numerous observations of central scotomata of restricted size, and it is also in full agreement with the results of the experiments upon the macular cortex (P. '33) and of the study of the minute structure of the retina in Primates (P. '35), both of which show that it is just the macula and the macular portion of the entire afferent visual system where the "projection" of the retina is most elaborate, where the size of its composing elemental structural-functional units is the smallest, where their number is the greatest, and where their separation from one another is farthest advanced or is most complete. In conclusion, let us call attention to the surprisingly large degree of visual function which was preserved in our ape although only a fraction of its total nervous-visual mechanism was left intact.

REFERENCES.

[1] Brouwer, B. "Ueber die Projection der Makula auf die Area striata des Menschen," *Journ. f. Psychol. u. Neurol.*, 1930, **40**, 147.

[2] *Idem.* "The Projection of the Retina on the Cerebral Cortex in Man." In "Localization of Function in the Cerebral Cortex," published by Assoc. for Res. in Nerv. and Ment. Dis., 1932, **13**, 529.

[3] Brouwer, B., and Zeeman, W. P. C. "The Projection of the Retina in the Primary Optic Neuron in Monkeys," *Brain*, 1926, **49**, 1.

[4] Holmes, G. "A Contribution to the Cortical Representation of Vision," *ibid.*, 1931, **54**, 470.

[5] *Idem.* "The Representation of the Mesial Sectors of the Retinæ in the Calcarine Cortex." *Jahrb. f. Psychiat. u. Neurol.*, 1934, **51**, 39.

[6] Juba, A. "Ueber das Projektionsfeld des zentralen Sehens im ausseren Kniehöcker und in der Sehrinde des Menschen," *Zeitschr. f. d. g. Neurol. u. Psychiat.* 1933. **147**, 121.

[7] Le Gros Clark, W. E., and Penman, G. G. "The Projection of the Retina in the Lateral Geniculate Body," *Proc. Roy. Soc.*, London, Ser. B., 1934, **114**, 291.

[8] Pfeifer, R. A. "Hirnpathologischer Befund in einem Fall von doppelseitiger Hemianopsie mit Maculaaussparung," *Journ. f. Psychol. u. Neurol.*, 1930, **40**, 319.

[9] Polyak, S. "The Main Afferent Fiber Systems of the Cerebral Cortex in Primates," University of California Press, Berkeley, California, 1932.

[10] *Idem.* "Projection of the Retina upon the Cerebral Cortex, based upon Experiments with Monkeys" In "Localization of Function in the Cerebral Cortex," published by Assoc. for Res. in Nerv. and Ment. Dis., 1932, **13**, 535.

[11] *Idem.* "A Contribution to the Cerebral Representation of the Retina," *Journ. Compar. Neurol.*, 1933, **57**, 541.

[12] *Idem.* "Structure of the Retina in Primates," *Acta Ophthalm.*, 1935, **13**, 52.

[13] *Idem.* "Minute Structure of the Retina in Monkeys and Apes," *Arch. Ophthalm.* (in print).

[14] Rönne, H. "Die anatomische Projektion der Macula im Corpus geniculatum ext.," *Zeitschr. f. d. g. Neurol. u. Psychiat.* (Orig.), 1914, **22**, 469.

THE PITUITARY-HYPOTHALAMIC MECHANISM: EXPERIMENTAL OCCLUSION OF THE PITUITARY STALK.

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INTRODUCTION.

THIS work is directed towards an elucidation of the rôle played by the hypophyseal stalk in linking the activities of the pituitary body and hypothalamus. The pituitary stalk has previously been regarded as a pathway for the secretion of the pars intermedia to the pars nervosa and base of diencephalon, and secondly as a possible mediator of nerve impulses from the hypothalamus to the pituitary body. It was believed that there existed a reciprocal interaction between certain of the hypothalamic nuclei and the pituitary gland and this has given rise to the conception of a pituitary-hypothalamic mechanism.

In the past experimental diabetes insipidus has been produced both by hypophysectomy (Vassale and Sacchi [31], Crowe, Cushing and Homans [8], and Richter [26]), and by isolated lesions of the hypothalamic nuclei (Aschner [1]), Camus and Roussy [7], Houssay [16], Bailey and Bremer [2], Bourquin [5 and 6]). The evidence has been reviewed extensively by Lhermitte [20], Roussy and Mosinger [27], Leschke [19], Staemmler [28] and Biggart [4], and appears equally in favour of the hypophysial and of the hypothalamic origin. With the gradual acceptance of the neural and vascular connections, an attempt has been made to bring together the two conflicting views. Thus Fisher, Ingram and Ranson [12] have recently brought forward evidence to show that in cats, injury of the tuber cinereum, causing bilateral destruction of the supra-optic-hypophyseal tract, results in atrophy of the supra-optic nuclei, atrophy of the posterior lobe, and a permanent upset in the water balance. They concluded that damage to this neural connection at any of three points, namely the nucleus, the fibre tract or the posterior lobe will produce experimental diabetes insipidus.

The results presented in this communication were obtained by complete obstruction of all pathways both for secretion and for nerve impulses between the pituitary body and the hypothalamus. The physiological findings show a striking difference in dogs and monkeys following the same procedure and there is a structural variation in the two species which accounts for this difference. The results show that the view put forward by Fisher, Ingram and Ranson for the cat is not applicable to the monkey and may therefore not be tenable in man.

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[1] While working as a Rockefeller Foundation Fellow.

PREVIOUS WORK ON OCCLUSION OF THE PITUITARY STALK.

Physiological studies following experimental division or occlusion of the pituitary stalk are few. Towards the end of his important monograph "L'Hypophyse du Cerveau," Paulesco [23] in 1908 reported briefly the results of experiments on six dogs in which the pituitary stalk had been divided and the gland left intact in the sella turcica. He concluded that such a procedure was equivalent to a total or nearly total hypophysectomy. In one of these animals, which succumbed within twenty hours following operation, the pituitary body was found turgid, hæmorrhagic and the cells in process of degeneration. Two others died within twenty hours of the operation, the remaining three living six, eighteen, and twenty-four days respectively. Except for brief mention of an immediate post-operative sleepy state and the absence of glycosuria in one of the series, no details were given of the post-operative course or post-mortem findings in these animals.

Crowe, Cushing and Homans [8] made an extensive study of experimental hypophysectomy in 1910 and reported five more dogs in which the pituitary stalk was divided. Two of these succumbed with all the symptoms of "cachexia hypophysiopriva," one on the tenth day and one after twenty-four days. Another animal was successfully tided over a period of threatened "cachexia hypophysiopriva" by injections of "anterior lobe extract," and lived five months, gradually increasing in weight but in all other respects apparently normal. The other two animals showed no tendency towards development of cachectic symptoms and were sacrificed on the twelfth and twenty-eighth post-operative days respectively, for histological purposes. In all cases marked degenerative and atrophic changes were found in the pituitary, most marked in the pars distalis, but in three animals which did not succumb to cachectic symptoms and which were ultimately sacrificed, persistent areas of normal-appearing epithelial cells were seen. The pars nervosa was usually more normal in size and was invaded by cells of the pars intermedia. There was an overabundance of hyaline throughout the pars nervosa and many colloid cysts in its epithelial investment. They interpreted their findings, so far as the pars distalis was concerned, as being due to interference with its major blood supply along the infundibular stalk. "The resultant condition . . . is almost the same as if this portion of the gland had actually been removed and then re-implanted like a graft, for the circulation is almost entirely cut off." In so far as the histological appearances of the pars nervosa were strongly suggestive of a damming back of colloid material, the experimental data of Crowe, Cushing and Homans appeared to fit in with the conception of secretion originating in the pars intermedia and passing through the pars nervosa and infundibular stalk to the base of the third ventricle.

Following these earlier studies on pituitary stalk section, Cushing and Goetsch [9, 10] adopted the method of placing a silver clip around the pituitary stalk, completely occluding any passage through it by tight compression. This was again carried out on dogs. Two out of the three animals subjected by them to this procedure showed post-operative glycosuria. In another, an extreme degree of polyuria persisted for a month. Histologically, the pituitary body showed the same appearances as had been described by Crowe, Cushing and Homans. The pars nervosa was found very cellular with a great increase of hyaline in the tissue spaces.

Karplus and Kriedl [17] were the first to separate the pituitary body from the hypothalamus in monkeys. Two animals lived several weeks without any obvious disturbances. The histological findings were not recorded. In 1911, Morawski [22] divided the pituitary stalk in six more monkeys. Two died within the first day, and of the remaining four which lived from six days to two months, no symptoms were noted. At post-mortem examination of these four animals, the pituitary body was reduced in size, the pars distalis being relatively larger and the pars nervosa smaller than normal. No histological changes were observed in the pars distalis but the pars nervosa showed increased cellularity. He compared his results with those of Biedl who had found in dogs that division of the stalk was as rapidly fatal as hypophysectomy and attributed the untoward experiences with dogs to an involvement of the third ventricle.

Later Bell [3] reported experiments on three dogs. The stalk was compressed in one and divided in two animals. They survived three to four months, all showing adiposity and, in two cases, genital dystrophy and somnolence in addition. Histological examination showed the cells of the pars distalis atrophied and widely separated. Dott [11] in 1923, repeated the experiment of division of the stalk, introducing a minute platinum plate between the pituitary body and the tuber cinereum in order to ensure the permanent deprivation of the main blood supply of the pars distalis. This procedure was carried out on three dogs. In all cases the characteristic syndrome ensued, viz., lethargy and adiposity, retardation of growth, lowering of temperature and degenerative changes in the thyroid and genital glands. All these symptoms could be attributed to the lack of an adequate blood supply. In addition Dott noticed a severe polyuria most marked during the first twenty-four to forty-eight hours. This he considered dependent upon an irritative stimulus to the pars intermedia by the presence of a foreign body.

In the Cameron lectures (1926), Cushing [10, *b*] reported some further experiments carried out in his laboratory by Maddock. Occlusion of the pituitary stalk by a clip resulted in a post-operative polyuria prolonged in character and a tendency to adiposity. The histological changes were the same as those previously reported in the paper by Crowe, Cushing and Homans.

METHOD.

The present study was carried out upon twenty dogs and twenty monkeys (*Macaca mulatta*). The ages of the dogs ranged from 6 weeks to 2 years and of the monkeys from 2 to 4 years. They lived in the laboratory in large metabolism cages for two to four weeks before any operative procedure was undertaken. Daily measurements were made of the fluid intake and urinary output. No direct estimation of fluids lost by way of intestines, skin and lungs was made but the "insensible loss" was calculated by computing the difference between the fluid intake and the urinary output. Diets were kept constant throughout the experiment. The basal metabolic rate, the blood-sugar content and the nitrogen and base constituents of the urine were estimated in the monkeys both before and after operation. This was carried out with the collaboration of Dr. N. Rakieten and Dr. M. B. Rheinberger to whom we are indebted.

Operative procedures.—All operations were carried out under sodium amytal anæsthesia given intraperitoneally, 0·5 to 0·6 c.c. of a 10 per cent. solution per kilogram of body-weight. In the monkeys the procedure was as follows:—

A large frontal parietal bone flap extending over the mid-sagittal line was turned down and more room was obtained by enlarging the bony opening deep into the temporal region. The dura was incised in curvilinear fashion parallel to the inferior line of the bone defect and the temporal lobe was carefully elevated. This brought into view the para-pituitary structures of which the oculomotor nerve and the internal carotid artery were the most prominent. Between these, the infundibulum could be clearly seen and a silver clip was applied to the pituitary stalk as far distally from the tuber cinereum as possible, and closed tightly. In three cases, the stalk was divided immediately below the site of the clip. The minute anatomy of the region varied and in some instances the exposure was improved by gentle retraction of the internal carotid artery forwards. For closure, the bone flap was replaced and the subcutaneous tissues approximated in two layers with interrupted silk sutures. The skin was secured with a continuous subcuticular suture of silk.

In dogs the exposure of the pituitary stalk was also carried out by the subtemporal approach after the zygoma and the temporo-parietal bones were removed on one side. The temporal muscle was employed so as to take the place of a bone flap in the closure. Within twelve hours the animals recovered sufficiently from amytal anæsthesia to begin drinking. During the preceding period of unconsciousness, the dogs passed considerable quantities of urine.

Thyroidectomies were performed in some of the dogs through a midline skin incision and care was taken to leave the parathyroid glands intact. The excised tissue was in all instances verified histologically. On no occasion was there any manifestation of tetany. The animals were surprisingly active after thyroidectomy and showed no gross signs of thyroid deprivation. There was, however, a remarkable and progressive loss of weight after removal of the thyroid.

Histological studies.—The animals were sacrificed at varying periods from three days to ten months after operation. Complete post-mortem examinations were performed on all animals. In half the cases, the tissues were fixed in situ by perfusion of 10 per cent. formol solution and the pituitary bodies were sectioned serially, some in the horizontal and others in the sagittal plane and stained with hæmatoxylin and eosin and Mann's stain. In those cases in which the tissues were not fixed by perfusion with formol, the hypothalamus was fixed in 95 per cent. alcohol and stained by the Nissl method.

Serial sections of the pituitary bodies and hypothalamus in normal monkeys and dogs were treated in a similar manner and served as controls for the histological studies.

RESULTS.

(1) *Metabolic Studies.*

Monkeys.—Occlusion of the pituitary stalk in monkeys did not result in polyuria or polydipsia. The average daily fluid intake and urinary output which before operation varied between 100 c.c. and 200 c.c. remained constantly at this level after operation. In two animals a puncture was made in the tuber cinereum two weeks after the pituitary stalk had been obstructed. In these instances the total daily intake and output rose to 500 c.c. on the first post-operative day, to 900 c.c. on the second post-operative day. It remained at this level for three days and then dropped rapidly to normal.

There was no significant alteration of the basal metabolic rate, the blood-sugar level, or the nitrogen and base constituents of the urine following occlusion of the pituitary stalk. The respiratory quotient which averaged 0·75 before operation remained constant. Blood-sugar readings ranged between 80 mgm. and 120 mgm. per cent. both before and after operation. The monkeys appeared in perfect health and showed no gross change in body-weight, character of hair, or general activity.

Dogs.—In dogs, occlusion of the pituitary stalk with a silver clip was invariably followed by extreme polyuria and polydipsia, which persisted for several weeks. In a previous communication [21] it has been shown that this effect is abolished by subsequent total thyroidectomy and can be re-established by oral administration of desiccated whole thyroid gland. Alternate states of extreme polyuria and oliguria could thus be produced at will. Total thyroidectomy had no demonstrable effect upon the daily fluid intake and output of the normal dog. In dogs with intact pituitary stalk, thyroid feeding had a mild diuretic action, which was, however, in no way comparable to the extreme polyuria and polydipsia produced by administration of thyroid gland after occlusion of the pituitary stalk. There appeared to be a severe imbalance in the water metabolism of the tissues apart from the renal mechanism in these experiments.

In order to study the effects of occlusion of the pituitary stalk in immature animals, puppies 6 to 7 weeks old were utilized. The procedure was followed by the usual diabetes insipidus, but in addition there occurred marked retardation of growth, sexual infantilism and subsequently extreme adiposity. This is illustrated in the following protocol:—

From a litter of mongrel puppies born in the laboratory, two females were chosen which, after seven weeks were approximately of equal size and weighed 2·7 kgm. and 2·9 kgm. respectively. For the week prior to operation, the average fluid intake for each animal was 400 c.c. daily and the average urinary output 150 c.c. On August 20, 1934, the pituitary stalk of one animal was occluded by means of a silver clip. The other puppy was kept under identical dietary and living conditions as a control Immediately following operation, the fluid intake rose to 2,200 c.c. daily and remained at a level of 1,600 c.c. for two weeks. It gradually decreased so that after five weeks it ran parallel with the control. The urinary output likewise increased directly after the operation to 1,500 c.c. and averaged about 1,200 c.c. daily for two weeks, falling gradually to the control level, so that after five weeks there was no further evidence of diabetes insipidus.

Although during the first ten weeks after operation there was no perceptible difference in the rate of growth of the two animals and the body-weights were approximately the same, five months after operation there was a marked disproportion in size and weight. The control litter mate weighed 10·8 kgm. The operated animal was considerably dwarfed in comparison and weighed only 6·4 kgm. It showed a slight tendency to adiposity and its coat was longer and of finer texture than that of its sister. Its head was small and the expression placid and mature and the animal showed none of the playful activity of the other puppy. From this time it became very markedly adipose and, though remaining dwarfed, gradually approached the body-weight of the control. Ten months after operation it weighed 12 kgm. while the control weighed 12·7 kgm. (fig. 1). On June 5, 1935, both animals were sacrificed for histological purposes. There were no abnormal findings in the control dog In the litter mate which had been operated upon, the most striking features apart from the changes in the pituitary body were the degree of adiposity and the genital infantilism. The subcutaneous fat, for instance, even over the sternum, measured 2·5 cm. in thickness. There was extreme hypoplasia of the uterus, vagina and ovaries.

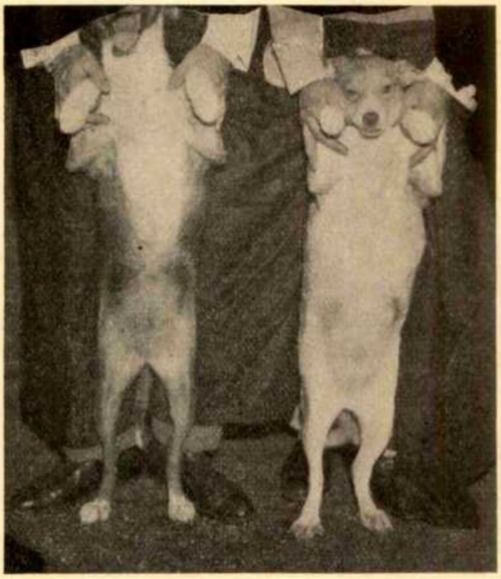

FIG. 1.—Littermate female puppies aged 12 months, to show dwarfism and adiposity ten months after occlusion of the pituitary stalk. Control animal on left.

Horizontal serial sections of the pituitary body showed disorganization of structure of the glandular part with marked decrease in the vascularity. On close examination the cells showed no granular formation in the cytoplasm. The cell outlines in many parts appeared to fuse. This glandular tissue with an incomplete lining of ciliated epithelium constituted the wall of a large central cavity. There were many small cysts of the same nature lying peripheral to the central cyst within which lay fragments of degenerated cells which had lost their nuclei. The pars nervosa appeared normal according to all criteria.

(2) *Histological Studies.*

In the monkey the pituitary body showed no real change in size or in the cyto-architecture of the glandular elements (fig. 2.) The vascularity of the pars distalis and pars tuberalis was unimpaired as seen in carmine gelatine preparations after the pituitary stalk had been clipped. The pars nervosa was not altered in size and was normal in appearance except for some increased cellularity which varied from case to case. The demonstrable colloid content did not vary appreciably from the normal.

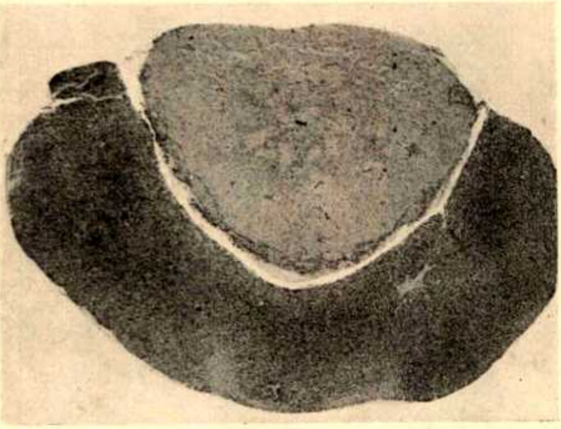

FIG. 2.—Horizontal section of primate pituitary body, two and a half months after occlusion of the pituitary stalk. No demonstrable alteration from the normal. (Mag. × 25.)

In dogs in which the pituitary stalk had been clipped there was an astonishing appearance for comparison (fig. 3). The pituitary body was not the normal pink round structure, but a flattened buff-coloured organ which was very friable and when ruptured, discharged a drop of oily brown fluid leaving a collapsed cystic shell. Microscopically, the wall of the cyst consisted of necrotic cells of the pars distalis, islets of cells remaining visible near the periphery where the blood supply appeared to be adequate. The carmine gelatine preparations showed almost complete avascularity of the tissues except in the peripheral parts where small blood-vessels were to be seen. The cysts had in part epithelial linings which were ciliated in some instances. The contents of he cyst appeared microscopically to be composed of débris and degenerated cells. In some cases no pars nervosa tissue could be recognized, while in others portions of the pars nervosa were found and, apart from some increased cellularity, showed no appreciable difference from the control. As in the monkey, there was no increase in colloid-like material in the glandular or nervous portions of the pituitary body.

The histological changes in the hypothalamus after occlusion of the pituitary stalk were similar in the dog and the monkey. The nuclei of the cells of the supra-optic and paraventricular nuclei showed the characteristic eccentricity, but not the shrinkage and hyperchromatosis diagnostic of retrograde cell change. The cytoplasm was pale with chromatin granules gathered at the periphery. Such an appearance, however, is frequently seen in the normal. Interspersed among the neurones were a larger number than usual of glial cells, often found in clusters surrounding the ganglion cells. Some of the latter appeared as merely shadowy forms, suggestive of degeneration. No demonstrable changes were observed in the tuberal or mammillary nuclei.

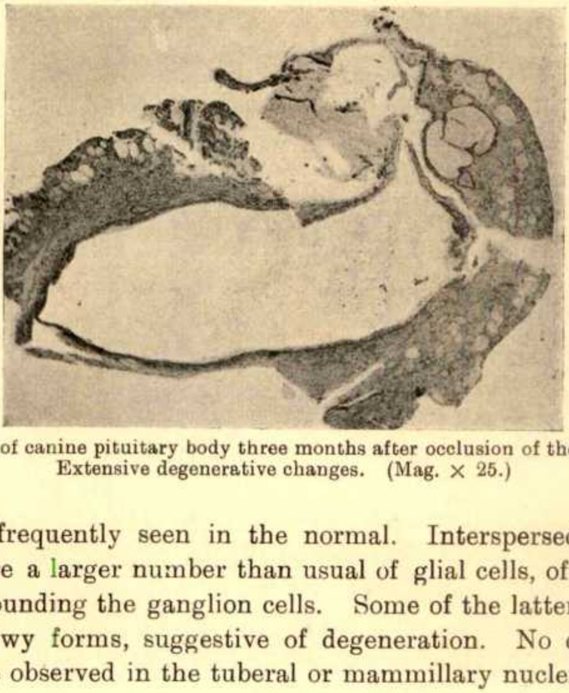

FIG. 3.—Section of canine pituitary body three months after occlusion of the pituitary stalk. Extensive degenerative changes. (Mag. × 25.)

DISCUSSION.

Experimental occlusion of the pituitary stalk as carried out in the present investigation accomplishes the complete obstruction to: (*a*) the pathway of secretion from the pituitary body to the hypothalamus along the stalk, either through the tissue spaces of the nervous portion or by way of the suggested portal circulation in the glandular part; (*b*) the transmission of impulses along the nerve connections in the stalk; and (c) the blood supply of the pituitary stalk reaching it along or in the stalk.

In the above experiments, occlusion of the pituitary stalk in the monkey resulted in no clear physiological evidence of failure of the pituitary hormones to reach the general circulation. This, together with the complete absence of any histological changes in the pituitary body in this animal is indicative that in the monkey at least, the passage of secretion along the stalk, if any, is not of great significance. This does not disprove the theory that the pituitary principle acts on hypothalamic centres, for it may still do so by means of the general circulation.

The existence of a bundle of unmyelinated fibres from the supra-optic and tuberal nuclei along the stalk into the pars nervosa seems to be fairly well established from the work of Ramon-y-Cajal [25], Hoenig [15], Tello [29], Trautmann [30], Pines [24], and Greving [14]. This tract is not well developed in the monkey. The fine thread-like nature of the stalk and the sparseness of nerve fibres passing along it do not suggest any striking neural connections between the pituitary body and hypothalamus. That such a tract activates the pars intermedia is still doubtful, and evidence in support of this view is lacking. The recent work of Karplus and Peczenik [18] is not wholly conclusive. After division of the pituitary stalk there are cellular changes in the supra-optic and paraventricular nuclei in some instances, but the changes consisting of pallor of some of the cells with a slight glial reaction around others, are difficult to interpret, for eccentricity of the nucleus and chromatolysis are no criteria of axonal division in the supra-optic and paraventricular nuclei.

In the present investigation the rich vascularity of the glandular portion in the monkey following occlusion of the stalk contrasted markedly with the almost complete avascularity and extensive necrotic changes of the corresponding part in the dog following this procedure. It is clear from these studies that clipping of the stalk occludes the major blood supply to the pituitary body in the dog and does not do so in the monkey. This accounts adequately for the retardation of growth and sexual infantilism observed in puppies and is in accordance with the view of Paulesco and Crowe, Cushing and Homans who described division or occlusion of the pituitary stalk in the dog as equivalent to a "complete or almost complete" hypophysectomy.

The reason for the difference in response of the water metabolism in the dog and monkey is not as clear. The results can be explained in one of two ways. The diabetes insipidus might be attributed to a lack of antidiuretic principle owing to degeneration of the pituitary of the dog. Such a view would be in accordance with all the histological findings in the present study. Hypophysectomy, however, has not been followed by diabetes insipidus in either the dog or the monkey, and in the latter, in the experience of the authors, hypothalamic lesions *after* previous hypophysectomy have resulted in severe upset of the water metabolism. Similarly, in the dog *after* hypophysectomy, Camus and Roussy have produced diabetes insipidus by a small lesion in the tuber cinereum. If, as Richter maintains, the essential and only factor necessary for the production of diabetes insipidus is a lesion severing the connection between the "posterior lobe" and the nuclei of the brain stem, provided that some "anterior lobe" tissue remains, then there is no clear explanation why the secondary lesion in the tuber cinereum after a previous hypophysectomy should be followed by polyuria. The fact that, in the monkey at least, the pars tuberalis spreads out under the tuber cinereum and is actually imbedded in the substance of this

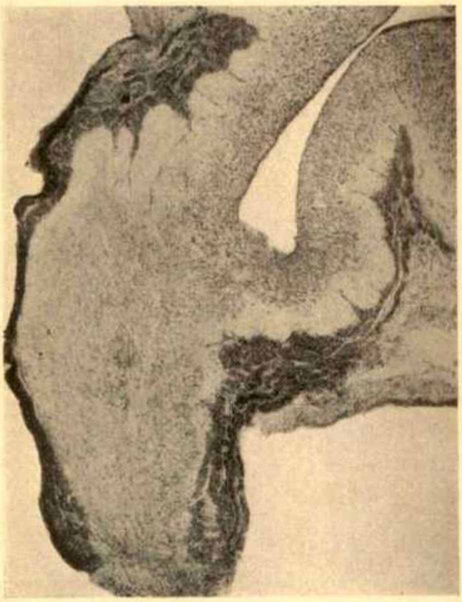

FIG. 4.—Coronal section of hypothalamus and proximal part of pituitary stalk in the monkey to show the pars tuberalis imbedded in the substance of the tuber cinereum. (Mag. × 100.)

part of the hypothalamus (fig. 4) is of great importance in this problem, for a complete hypophysectomy (including the pars tuberalis) is obviously impossible without destruction of the tuber cinereum. In view of this fact the clear distinction drawn between hypophysectomy and a strictly hypothalamic lesion by earlier workers in this field is not feasible and many of their conclusions cannot therefore be accepted as absolute.

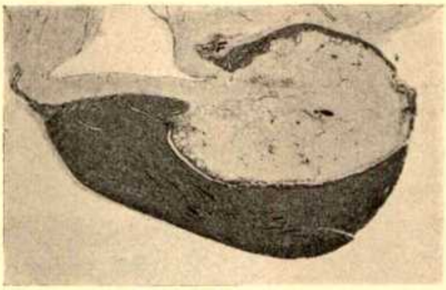

FIG. 5.—Sagittal section of canine pituitary-hypothalamic block injected with carmine gelatine mass, showing the short thick pituitary stalk containing direct prolongation of the third ventricle. (Mag. × 17.)

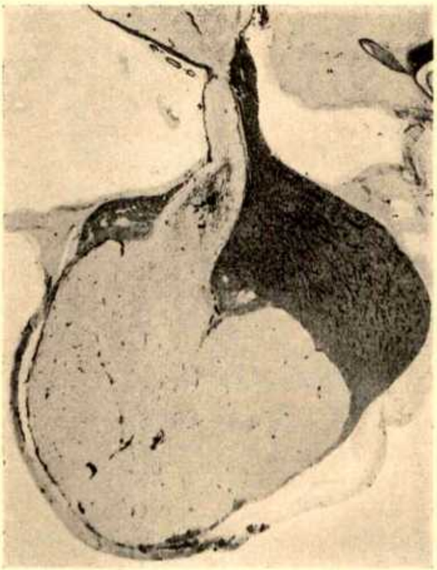

FIG. 6.—Sagittal section of the pituitary-hypothalamic block of the monkey injected with carmine gelatine mass, showing the long thread-like nature of the pituitary stalk. The third ventricle does not extend beyond the tuber cinereum. (Mag. × 25.)

The second explanation which might be offered for the extraordinary difference in the behaviour of the fluid exchange in the dog and the monkey is injury to hypothalamic centres. There is an important anatomical difference in this region in the two species. In the dog the pituitary stalk is short, thick, and contains a direct prolongation of the third ventricle, so that in this animal the stalk and tuber cinereum are identical (fig. 5). In the monkey, on the other hand, the stalk is comparatively a long thread-like band connecting the clearly differentiated tuber with the pituitary body, and the relations are such that it is possible to place a silver clip around the stalk without injuring the adjacent structures (fig. 6). Furthermore, in this animal, the third ventricle ends in the tuber cinereum proper and does not extend into the stalk. In the dog, therefore, the lower hypothalamic centres are damaged somewhat by the silver clip and are certainly not involved in the monkey. Such an explanation would appear to fit all the known facts, although it still leaves unexplained the anti-diuretic action of pituitrin on experimental diabetes insipidus.

SUMMARY.

1. Complete obstruction to the passage of secretion and nerve impulses between the pituitary body and hypothalamus was accomplished by the application of a silver clip to the pituitary stalk in the dog and the monkey.

A striking difference was subsequently observed in the two species.

2. Whereas in the dog there followed a state of diabetes insipidus which was abolished by thyroidectomy and re-established by oral administration of thyroid gland, no polyuria or polydipsia occurred in the monkey. The hypothesis of Fisher, Ingram and Ranson is therefore not applicable to the latter animal.

3. The basal metabolic rate, the blood-sugar level and the nitrogen and base constituents of the urine were unaltered in the monkeys.

4. Metabolic changes were manifested in puppies by retardation of growth, sexual infantilism, adiposity, refinement of hair and sluggish general behaviour.

5. The canine pituitary showed marked degenerative changes due to interference in the major blood supply as revealed by carmine gelatine preparations. No comparable changes either in vascularity or in cyto-architecture were demonstrable in the primate pituitary.

6. There is an important anatomical difference in the pituitary stalk and in the downward extension of the third ventricle in the two species.

7. It is concluded that in the monkey obstruction of the pituitary stalk does not interfere with the nourishment of the pituitary body or with discharge of the pituitary hormones into the general circulation..

8. The metabolic responses in the dog have been attributed in the past either to a pituitary or to a hypothalamic disturbance, but the inseparable anatomical arrangement of the pituitary-hypothalamic complex does not warrant such a clear distinction on experimental grounds. In the monkey the evidence supports the hypothalamic origin of diabetes insipidus.

REFERENCES.

[1] Aschner, B. (*a*) "Ueber die Funktion der Hypophyse," *Arch. f. d. ges. Physiol.*, 1912, **146**, 1-146; (*b*) "Hypophyse und Diabetes Insipidus," *Munch. med. Wochenschr.*, 1917, **64**, 81.

[2] Bailey, P., and Bremer, F. "Experimental Diabetes Insipidus," *Arch. Int. Med.*, 1921, **28**, 773-803.

[3] Bell, W. B. "The Pituitary," New York, 1919.

[4] Biggart, J. H. "Diabetes Insipidus," *Brain*, 1935, **58**, 86-96.

[5] Bourquin, H., Benesh, L., and Lanam, M. "Studies on Diabetes Insipidus. I." *Amer. Journ. Physiol.*, 1927, **79**, 362-376.

[6] Bourquin, H. "Studies on Diabetes Insipidus. II." *Ibid.*, 1927, **83**, 125-133; "Studies on Diabetes Insipidus. III." *Ibid.*, 1929, **88**, 519-528; "Studies on Diabetes Insipidus. IV." *Ibid.*, 1931, **96**, 66-77.

[7] Camus, J., and Roussy, G. (*a*) "Présentation de sept chiens hypophysectomisés depuis quelques mois," *Compt. Rend. Soc. Biol.*, 1913, **74**, 1386-1388; (*b*) "Diabète insipide expérimental," *Ibid.*, 1920, **83**, 764-765, 901-902, 1578-1583; (*c*) "Experimental Researches on the Pituitary Body," *Endocrinology*, 1920, **4**, 507-522; (*d*) "Les fonctions attributées à l'hypophyse," *Journ. d. Physiol. et de Pathol.*, 1922, **20**, 509-518, 535-547; (*e*) "Les syndromes hypophysaires," *Rev. Neurol.*, 1922, **29**, 622-637.

[8] Crowe, S. J., Cushing, H., and Homans, J. (*a*) "Effects of Hypophyseal Transplantation Following Total Hypophysectomy in the Canine," *Quart. Journ. Exper. Physiol.*, 1909, **2**, 389-400; (*b*) "Experimental Hypophysectomy," *Bull. Johns Hopkins Hosp.*, 1910, **21**, 127-169.

[9] Cushing, H., and Goetsch, E. "Concerning the Secretion of the Infundibular Lobe of the Pituitary Body and its Presence in the Cerebrospinal Fluid," *Amer. Journ. Physiol.*, 1910, **27**, 60-86.

[10] Cushing, H. (*a*) "Concerning Diabetes Insipidus and the Polyurias of Hypophyseal Origin," *Bost. Med. and Surg. Journ.*, 1913, **168**, 901-910, (*b*) "Studies on Intracranial Physiology and Surgery," Oxford University Press, London, 1926, 1-146; (*c*) "Papers relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System," Thomas, Springfield, 1932, 1-234; (*d*) "Posterior Pituitary Activity from an Anatomical Standpoint," *Amer. Journ. Path.*, 1933, **9**, 539-547.

[11] Dott, N. M. "An Investigation into the Functions of the Pituitary and Thyroid Glands," *Quart. Journ. Exper. Physiol.*, 1923, **13**, 241-282.

[12] Fisher, C., Ingram, W. R., and Ranson, S. W. "Relation of Hypothalamico-hypophyseal System to Diabetes Insipidus," *Arch. Neur. and Psych.*, 1935, **34**, 124-163.

[13] Gemelli, A. (*a*) "Sur la fonction de l'hypophyse," *Arch. Ital. de Biol.*, 1908, **50**, 157-174; (*b*) "Ulteriore contributo alla fisologia dell' ipofisi," *Folia. Neurobiol.*, 1908, **2**, 167-196.

[14] Greving, R. (*a*) "Zur Anatomie, Physiologie und Pathologie der vegetativen Zentren im Zwischenhirn," *Ergebnisse der Anatomie und Entwicklung*, 1923, **24**, 348-418; (*b*) "Beiträge zur Anatomie der Hypophyse und deren Funktion," *Deutsch. Zeitschr. f. Nervenheilk.*, 1926, **89**, 179-194; (*c*) "Beitrage zur Anatomie der Hypophyse und deren Funktion." II. Mitteilung. *Zeitschr. f. d. ges. Neur. u. Psychiat.*, 1926, **104**, 466-479.

[15] Hoenig, O. "Untersuchungen zur Histologie der Hypophyse," *ibid.*, 1922, **79**, 197-209.

[16] Houssay, B. A. "The Pituitary Body and Polyuria," *Endocrinology*, 1918, **2**, 94-97.

[17] Karplus, J., and Kreidl, A. "Operationen am uberhängenden Gehirn," *Wiener klin. Wochnschr.*, 1910, **23**, 309-310.

[18] Karplus, J. P., and Peczenik, O. "Uber die Beeinflussung der Hypophysentatigkeit durch die Erregung des Hypothalamus," *Arch. f. d. ges. Physiol.*, 1930, **225**, 654-668

[19] Leschke, E. "Diabète insipide et système hypothalamo-hypophysaire," *Ann. de Med.*, 1933, **33**, 261-271.

[20] Lhermitte, J. "La polyurie infundibulaire, le diabète insipide syphilitique," *ibid.*, 1922, **11**, 89-127.

[21] Mahoney, W., and Sheehan, D. "The Effect of Total Thyroidectomy upon Experimental Diabetes Insipidus in Dogs," *Amer. Journ. Physiol.*, 1935, **112**, 250-255.

[22] Morawski, J. "Die Durchtrennung des Hypophysenstieles beim Affen., *Zeit. f. d. ges. Neur. u. Psychiat.*, 1911, **7**, 207-218.

[23] Paulesco, N. C. "L'Hypophyse du Cerveau," Paris, 1908..

[24] Pines, J. (*a*) "Ueber die Innervation der Hypophysis cerebri" (Mit. I), *Journ. f. Psychiat. u. Neurol.*, 1925, **32**, 80-88; (*b*) "Ueber die Innervation der Hypophysis cerebri" (Mit. II), *Zeit. f. d. ges. Neur. u. Psychiat.*, 1926, **100**, 123-138; (*c*) "Ueber die Innervation der Hypophysis cerebri," *ibid.*, 1927, **107**, 507-511.

[25] Ramon-y-Cajal, S. "Estructura del ganglio de la habenula de los mamiferos," *An. Soc. Españ. Hist. Nat.*, 1894, S. 2, **23**, 185-237.

[26] Richter, C. P. (*a*) "Experimental Diabetes Insipidus," *Brain*, 1930, **53**, 76-85; (*b*) "Experimental Diabetes Insipidus: its relation to the Anterior and Posterior Lobes of the Hypophysis," *Amer. Journ. Physiol.*, 1934, **110**, 439-447.

[27] Roussy, G., and Mosinger, M. "Le tuber cinereum et son rôle dans les principales fonctions du metabolisme," *Ann. de Méd.*, 1933, **33**, 193-238.

[28] Staemmler, M. "Diabetes Insipidus und Hypophyse," *Ergebn. d. allg. Path. u path. Anat.*, 1932, **26**, 59.

[29] Tello, F. "Algunas observationes sobre la histologiá de la hipófisis humana," *Trab. d. lab. de invest. biol. Univ. de Madrid*, 1912, **10**, 145-183.

[30] Trautmann, A. "Anatomie und Histologie der Hypophysis cerebri einiger Säuger," *Arch. f. mik. Anat.*, 1909, **74**, 311-367.

[31] Vassale, G., and Sacchi, E. "Sulla distruzione della gliandola pituitaria," *Riv. sper. di Freniat. Regguio-Emilia*, 1892, **18**, 525-561.

THE EFFECTS OF LESIONS OF THE DORSAL COLUMN NUCLEI IN THE MACACUS RHESUS.

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I.—INTRODUCTION.

As a sequel to the findings which we have reported in this Journal [1, 2] on the effects of section of the dorsal columns and the restiform body, we are now presenting a report of the effects of lesions of the gracile and cuneate nuclei as the next step in an analysis of sensory and cerebellar pathways.

II.—REVIEW OF THE LITERATURE.

There are relatively few reports of experiments dealing with the effects of lesions of the gracile and cuneate nuclei. Bechterew (1890) [3] noted a severe disturbance of equilibrium in a few dogs in which he made wounds in these nuclei. The dogs showed lateropulsion with falling. The disturbance was greater when the animals were blindfolded. No sensory abnormalities were described.

Ferrier and Turner (1894) [4] described the behaviour of monkeys in which they destroyed both gracile and cuneate nuclei. When the nucleus gracilis or clavate nucleus of one side was destroyed the animal showed a tendency to fall backward to either side; there was considerable swaying on exertion, and in walking the limb movements were slightly sprawling. The head was retracted and the chin was turned to the side of the removal. The knee-jerks were active and equal. Examination revealed complete retention of the sensibility to touch, pain and localization. One week after operation the animal was reported as being difficult to distinguish from a normal monkey. It jumped and climbed readily. Histological controls of the lesions were described.

F. W. Mott (1895) [5] reported experiments on monkeys in which he cut the afferent fibres on one side as they left the gracile and cuneate nuclei. He reported difficulty in observing the physiological effects, but he stated that extensive lesions were associated with inability of the animal to use the ipsilateral limbs, and with diminution of sensation on the side of the lesion. W. A. Turner (1895) [6] reported on the localized destruction of the tubercle of Rolando in five monkeys. We mention his findings because of the fact that the cuneate nucleus was usually included in the lesions. None of the clinical manifestations was attributed by the author to the involvement of the cuneate nucleus.

Tschermak (1898) [7] studied the effects of lesions of the dorsal column nuclei in cats. In three animals he destroyed these nuclei on one side. By the first or second day after the operation they made attempts to walk, in which attempts, however, they swayed and fell toward the side of the lesion, particularly if they attempted to raise the feet. Later, the animals did not fall toward the involved side but could be easily pushed over on to that side. In walking the contralateral limbs were used firmly, but the ipsilateral legs were considerably abducted, and the fore-foot was used clumsily and was often placed with the dorsum downward. On sitting up all three animals swayed toward the side of the operation. There were no disturbances of touch, pain and localization. All the symptoms decreased rapidly and after two, or at most five days, they had practically disappeared. In one case, however, there was a noticeable disability even up to death after sixteen days. The author felt that many of the symptoms observed by him could be accounted for by a disturbance of the sense of position and of movement of the limbs, i.e. of the so-called muscle sense. Serial sections of the material revealed destruction of the posterior two-thirds of the dorsal column nuclei of one side. The substantia gelatinosa was also involved in the lesion, and the nucleus of the 12th nerve was usually destroyed. In the caudal portion of the wound the dorsal as well as the most cephalic portions of the pyramidal decussation were injured. Above the lesion the restiform body and the lemniscus were degenerated.

Probst (1902) [8] reported on the effects of lesions of the dorsal column nuclei in dogs and cats. He compared the effects of such lesions to those resulting from lesions of the cerebellum. Following a right-sided lesion of the nuclei, the dog fell to the left and presented ataxia and disturbances in equilibrium. There was also a tendency to fall over backwards. In the acute phase the dog maintained the ipsilateral fore-limb in tonic flexion and often placed the limb on the floor with the dorsum downwards. Because of the tonic flexion the fore-limbs were often crossed. Some degree of paresis of the ipsilateral fore-limb persisted even to the 15th day. According to the author such paresis resembled that following removal of the cortical motor area and was based upon a loss of muscle sense. The pupils did not react well. The knee-jerks were active. The dog did not react to pin-pricks.

Mussen (1927) [9], in reporting on cats in which the nuclei graciles et cuneati were cauterized, claimed that the characteristic symptom was a loss of the postural sense involving joints of one or more limbs. Equilibrium was but slightly disturbed and pain and touch sensation were normal. In one case with right-sided destruction of the nuclei loss of sense of position was indicated by the animal frequently resting on the dorsum of the right fore-limb. Any abnormal posture in the hind limbs would be corrected at once. In his cases the disabilities, which were interpreted as indicating loss of sense of position, had not disappeared at the end of three weeks. Unfortunately we have not been able to find descriptions of the exact extent of the lesions in his cases.

III.—METHOD IN OUR EXPERIMENTAL WORK.

Macacus rhesus monkeys were used in all the experiments. In all twenty-one animals were used. The operations consisted of unilateral or bilateral destruction of the gracile and cuneate nuclei, unilateral destruction of the nucleus gracilis or of the nucleus cuneatus, and lesions of these nuclei in combination with other lesions, e.g. of the spino-cerebellar tract or the inferior cerebellar peduncle.

The monkey was placed in position on the table so that the head and neck extended over the end of the table, enabling the operator to flex the head on the chest. Under deep ether anæsthesia, with usual surgical aseptic technique, the muscles of the neck were split in the mid-line and held apart with an automatic retractor. The occipital bone was cleared of muscular attachments and the arch of the atlas was exposed. The occipital bone was removed well up over the transverse sinuses. Usually the arch of the atlas was removed. The occipito-atlantoid ligament and the dura over the cerebellum were split and retracted, exposing the caudal portion of the vermis, portions of the lateral cerebellar lobes and the upper portion of the spinal cord. The arachnoid was opened and the region of the obex carefully cleared of attachments of arachnoid. The vermis was retracted upward with a small flat retractor and the nuclear groups could then be clearly seen. The various lesions were made usually with a small ophthalmic knife or capsulotome, which made it possible to cut out a small mass of tissue which was then removed with fine forceps and eye scissors. In a few cases the lesion was made with a small sharpened Spratt's curette, or with a hot needle and finally in one or two cases by injecting a drop or two of alcohol with a 25 gauge bent needle. The dura was not sutured in closing. The muscles were approximated with catgut or black silk sutures and the wound was closed with Michel skin clips. With this simple technique we experienced no difficulty in any of our animals, as regards either infections or marked spreading of the lesion, except in the widely destructive lesions involving both gracile and cuneate nuclei. It is of interest that out of five animals in which the complete bilateral lesion was attempted at one stage, three died after an apparently normal recovery up to three days when they suddenly became ill and usually died on the fourth day. Post-mortem examinations revealed pneumonia in all cases. The lesion probably had spread to involve the nuclei of the vagus. The animals with smaller surgical lesions or complete unilateral involvement were usually up and about the cage in an hour, or at most two hours, after the operation. The two animals which survived complete bilateral lesions were very weak for three or four days after the operation, but once they passed this point they improved rapidly.

The animals were usually killed for study with the Marchi or the Weigert stains, the Marchi stain requiring sacrifice of the animal from the eleventh to the sixteenth day and the Weigert requiring at least six weeks survival. Serial sections of the brain-stem frontal to the upper cervical cord were studied in each of these animals with one or other of these methods. A complete anatomical report of the degenerations resulting from these lesions will be reported elsewhere in a study of the connections of the posterior column nuclei. In the present paper, we are concerned mainly with the symptoms following the various experiments and with a presentation of the essential features of the anatomical lesions.

IV.—Experimental Material.

In all, twenty-one monkeys were used in these operations on the dorsal column nuclei. The protocols to be presented will include one of each of the various pure types: (*a*) Unilateral destruction of the nucleus gracilis and the nucleus cuneatus; (*b*) unilateral destruction of the nucleus gracilis; (*c*) unilateral destruction of the nucleus cuneatus; (*d*) bilateral destruction of the nuclei graciles et cuneati.

Protocol No. 1.—Cer. 57.

Operation, November 22, 1932: *Destruction of the right dorsal column nuclei.*—Usual technique as described above. Very little bleeding. The lesion appeared well confined to the nuclei at operation. When the animal came out of the anæsthesia there was a sharp twist of the chin to the right, but no other abnormality.

Three hours after operation.—The animal is now well out of the anæsthesia and is sitting up in the cage eating a piece of orange. The rotation of the chin to the right which was present for about one hour after the operation has disappeared and the posture of the head is now normal. The animal usually sits with the right side of the body against the cage. When it sits on the floor without the support of the cage it shows a slightly flexed and adducted posture in the right fore-limb with some abduction in the right hind-limb giving a broad base to the hind-limbs. In this sitting posture there is no side-to-side swaying of the animal. If it is teased with a small stick it reaches out and takes the stick with the left hand only, no grasping efforts being made with the right limbs. There is no abnormality in the reactions of the eyes nor spontaneous nystagmus. No evidence of facial paralysis, or any signs of vestibular dysfunction are observed. The animal seems to be able to swallow and to protrude the tongue. In the sitting posture the most definite disability at this time seems to be a marked loss of spontaneous use of the right limbs. The disability seems to be of the same type as that seen in lesions of the dorsal columns and consists of hypotonia and a lack of spontaneous grasping, but the deep reflexes are active. All of the disabilities are more accentuated in the right fore-limb, which remains practically unused in movements of locomotion, reaching, climbing or in any type of movement requiring spontaneous activity with the limb. The right hind-limb is held slightly flexed, but it is used awkwardly in walking, with jerkiness and lack of co-ordination. It is not employed, however, for active grasping. The gait is practically three-legged, since the right fore-limb is not used. At times the animal rests on the right fore foot with the dorsum of the foot downward. In climbing the animal uses the left limbs practically alone. Gross attempts at catching hold of the support, however, are made with the right limbs, particularly the hind-limb, but the animal seems to be unsuccessful in actually grasping firmly the cage or object of support. Muscle tone diminished in both right limbs. The hypotonia is greater in the fore-limb. So far as can be determined at this stage there does not seem to be any loss of response to pain or touch or of localization of touch. When the animal is dropped head first with the eyes open there is some extension of all limbs, but the right fore-limb is extended much less actively than the left fore-limb. The left limbs appear normal. The hopping and placing reflexes are diminished on the right. The vestibular or labyrinthine reflexes are normal.

November 23: twenty-four hours after operation the condition was unchanged. It is of interest to note here how this animal differs at this stage from animals at a similar stage with lesions of the spino-cerebellar system in the medulla. This animal shows absence of spontaneous grasping and active deep reflexes, in contrast to the normal grasping and hypo-reflexia of the spino-cerebellar animal. In addition, no falling toward the side of the lesion occurs, whereas this is the usual finding when the spino-cerebellar tracts are divided.

November 29: One week after operation. The animal has improved considerably during the past week, but the phenomena which were present at the three hour-stage persist, though slightly less intense. The only sensory abnormality which can be determined is the response of the animal to passive movement of the limbs when the eyes are covered. Then it makes no attempt to correct changes in the position of the right limbs, whereas vigorous attempts are made when the left limbs are moved. When the animal runs, jumps about, or climbs along a pipe or a bar, the disability in the right side becomes clearer. It consists essentially of the animal's inability to use the right limbs for actively grasping the object of support. At times the right fore-limb is used for encircling the support with the upper portions of the extremity, but the object is never grasped spontaneously with the fingers or hand. It is of interest, however, that if the hand is placed around a small bar and the animal is then suddenly allowed to drop while blindfolded, it may grasp the bar and remain hanging for a considerable time, showing that a reflex type of grasping may occur in the involved limbs. Testing of vestibular function, done with Dr. Northington,

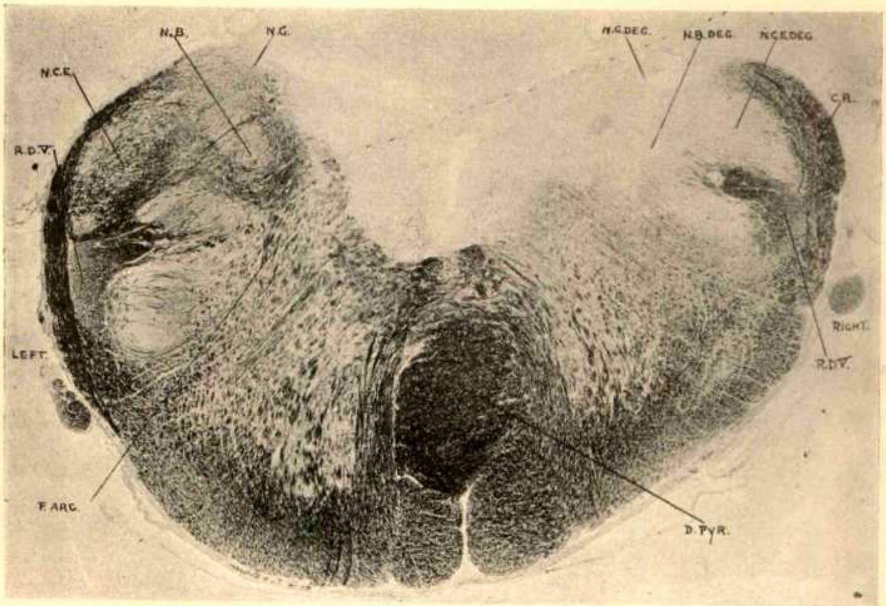

FIG. 1.—Section of medulla at level of pyramidal decussation. Weigert preparation. On the right there is seen to be a complete disappearance of the nucleus gracilis, the nucleus cuneatus and the dorsal portion of the external cuneate nucleus, all of which have been replaced by degenerated tissue. There is a complete absence of arcuate fibres from the nuclei on the right side. The section is somewhat oblique, the dorsal portion being at a more cephalic level than the ventral. N.G., nucleus gracilis; N.B., nucleus cuneatus; N.C.E., external cuneate nucleus; R.D.V., descending root of the 5th nerve; F.Arc., arcuate fibres; D.Pyr., pyramidal decussation; C.R., corpus restiforme; Deg. (after initials), degenerated.

shows no evidence of involvement of the vestibular apparatus. The swimming of the animal appears unaffected.

December 6: Two weeks after operation the condition was the same.

December 22: One month after operation. The animal has improved considerably. However, on careful examination it is seen to present essentially the same disabilities as were present at the earlier stage. The right fore-limb, for example, is practically never used for active grasping movements such as for picking up food; at the most it is employed in gross supporting movements.

A slightly flexed posture and some degree of hypotonia still persist. The right hind-limb has improved and is used quite well in walking, but occasionally the toes may be turned under the sole of the foot without any attempt on the part of the animal to correct the posture. Extension of the limb on falling, and the placing and hopping reflexes have improved considerably. There is no clinical evidence of vestibular dysfunction. At this stage the essential deficiencies are in the ability for active accurate grasping with the right limbs, especially with the fore-limb and diminution of the sense of position. This is a picture closely resembling that seen in right sided hemisection of the dorsal columns in the high cervical region.

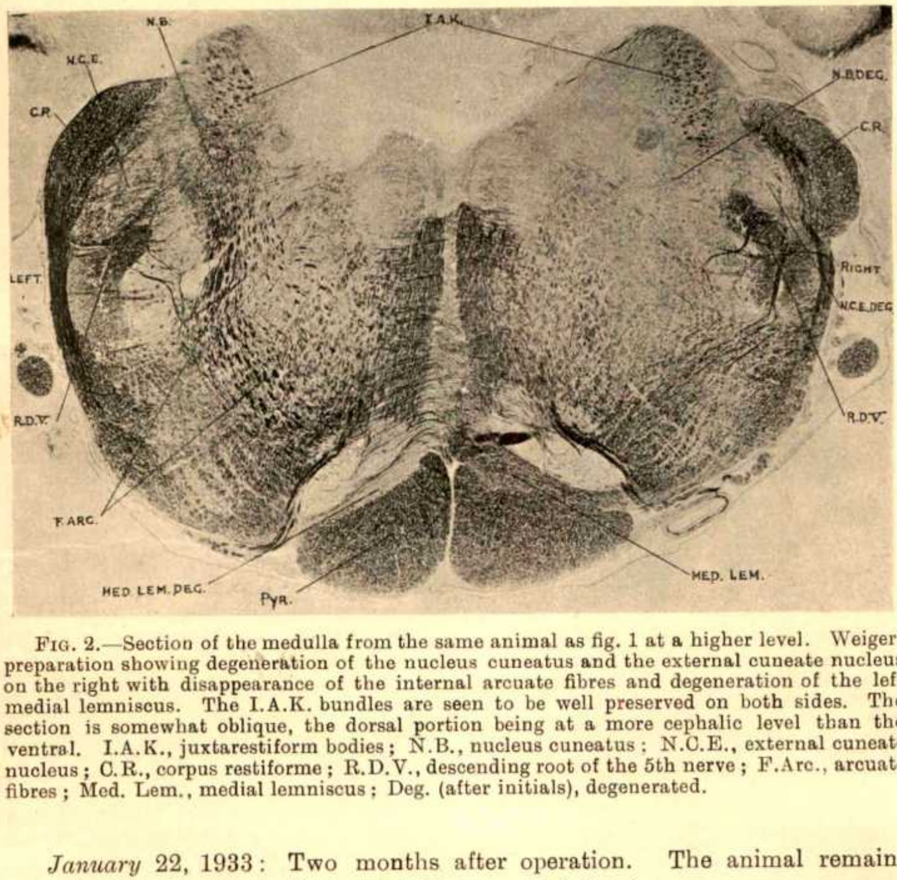

FIG. 2.—Section of the medulla from the same animal as fig. 1 at a higher level. Weigert preparation showing degeneration of the nucleus cuneatus and the external cuneate nucleus on the right with disappearance of the internal arcuate fibres and degeneration of the left medial lemniscus. The I.A.K. bundles are seen to be well preserved on both sides. The section is somewhat oblique, the dorsal portion being at a more cephalic level than the ventral. I.A.K., juxtarestiform bodies; N.B., nucleus cuneatus; N.C.E., external cuneate nucleus; C.R., corpus restiforme; R.D.V., descending root of the 5th nerve; F.Arc., arcuate fibres; Med. Lem., medial lemniscus; Deg. (after initials), degenerated.

January 22, 1933: Two months after operation. The animal remains essentially stationary, still showing the same deficiencies.

February 22: Three months after operation, the condition was the same.

May 22: Six months after operation. The disinclination to use the right arm in reaching for food, in climbing, or in any type of the finer spontaneous grasping movements has persisted up to the present. Definitely co-ordinated movements of the fingers are not observed. The right hind-limb is used to considerable advantage, although here again the finer grasping movements are not well performed. Muscle tone is still diminished on the right side. The deep reflexes are active. No sensory defects are found except a failure to respond promptly to change in position of the right limbs. The animal was killed at this chronic stage for study with the Weigert stain.

Anatomical Report.—Serial sections with the Weigert stain revealed complete destruction of the nucleus gracilis and nucleus cuneatus on the right side and some cicatricial involvement of the nucleus gracilis on the left. This was not marked, however, and was confined to the dorsal portion of the nucleus. On the right, the lesion had involved all elements of the nuclei gracilis et cuneatus in addition to a portion of the external cuneate nucleus (nucleus of Clarke-Monakow) (figs. 1 and 2). On this side the absence of arcuate fibres, due to destruction of their nuclei of origin, was in marked contrast with the left side, where the intact arcuate fibres could be clearly seen. Sections in the spinal cord below the lesion showed no degeneration in the pyramidal tracts. Above the lesion (fig. 3) there was a complete degeneration of the left medial lemniscus which arose from the right nuclei gracilis et cuneatus. Because of the involvement of Clarke-Monakow's nucleus on the right, the restiform body above the lesion appeared slightly paler than did the normal left side. The vestibular

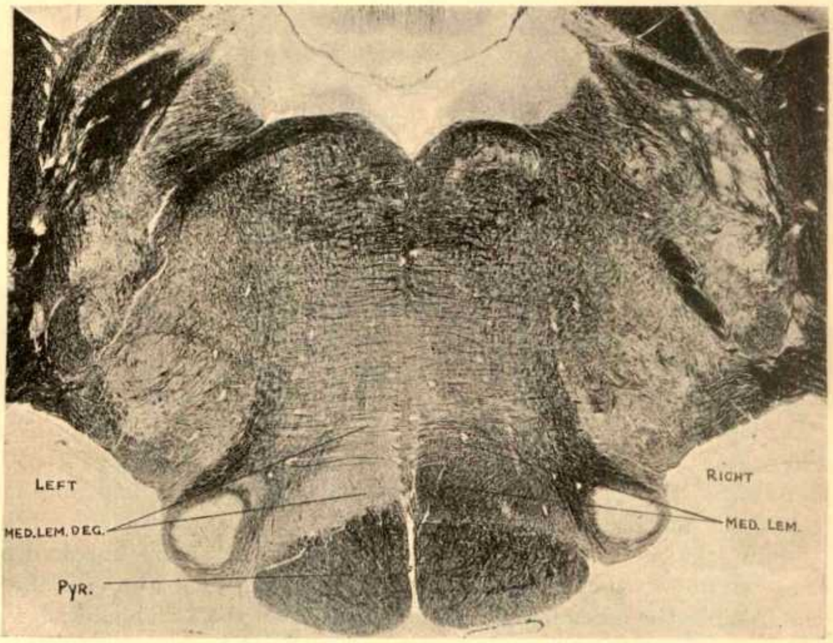

FIG. 3.—Section of the medulla from the same case as figs. 1 and 2, but at a considerably higher level, showing the complete degeneration of the medial lemniscus on the left. Weigert preparation. Med. Lem., medial lemniscus; Pyr., pyramid; Deg. (after initials), degenerated.

nuclear system and the I.A.K. system (juxtarestiform body) appeared well preserved on both sides.

In summary, the case anatomically presents a complete destruction of the right nuclei gracilis and cuneatus and of a portion of Clarke-Monakow's nucleus, with degeneration in the opposite medial lemniscus owing to destruction of the first two nuclei. There is also slight involvement of the left nucleus gracilis.

Protocol No. 2—*Monkey Cer.* 139.

Operation, January 4, 1934 : *Lesion of the left nucleus gracilis.*—On coming out of the anæsthesia there was no abnormal posture of the head or limbs.

Three hours after operation.—With the animal well out of the anæsthetic there is very little abnormal in its behaviour. The most important finding at this time is a slight weakness on the left side with relative disuse of the left limbs, especially in active grasping movements. The involvement in the left fore-limb is very slight and inconstant. The left hind-limb is used but appears clumsy. At times when the animal sits up, the left hind-limb is abducted and the toes of the left hind foot occasionally turn in under the foot without the animal appearing to notice it. The animal uses both fore-limbs in reaching for food, although slight preference is given to the right. Muscle tone is diminished in the left hind leg. The knee-jerks are active on both sides, possibly slightly more active on the left. All the special reflexes, including the righting, position and labyrinthine reflexes are normal, except the hopping and placing reflexes which are somewhat diminished in the left hind-limb. The animal responds to pinching, deep pressure and superficial touch in all the limbs and the trunk and head. It appears to be aware, when blindfolded, of changes in the position in all limbs except in the left hind-limb in which relatively greater excursions can be made without apparent awareness by the animal. When the animal jumps from a high place the left hind-limb tends to slip on landing. On climbing there is very little disability, apart from a slight clumsiness or awkwardness and failure to place the left hind-limb accurately. The more the animal climbs about now the more exact it becomes with the left fore-limb. The effect on this limb is merely temporary.

To summarize, in the acute stage we find an inco-ordination and some diminution in the sense of position in the left hind-limb, associated with a diminution in muscle tone, retention of sensation, diminution in hopping and placing reflexes, and an active knee-jerk. There is a slight involvement of a similar kind in the left fore-limb.

January 5, 1934.—Twenty-four hours after operation. The condition is unchanged except that the involvement of the left fore-limb seems to have completely disappeared. The animal now uses both fore-limbs indiscriminately for picking up food, for climbing, or catching flies.

January 11.—One week after operation. During the past week the animal has improved so much that, except for slight instability of the left hind leg in climbing, diminution in the hopping reflex response, slight weakness in jumping and some hypotonus and active deep reflexes in this limb, the animal appears normal. Both fore-limbs have been equally well used in reaching for food.

January 15.—Eleven days after operation. The condition of the animal is essentially the same. The animal was killed on this date for study by serial Marchi preparations.

Anatomical Report.—The lesion was confined essentially to the nucleus gracilis on the left. Fig. 4 illustrates a section at the level of the lesion showing the destruction of the nucleus gracilis, and slight involvement of the most caudal and medial portion of the nucleus cuneatus. A few of the most dorso-medial fibres of the funiculus cuneatus were also injured as they passed the dorso-lateral border of the nucleus gracilis at its caudal extremity. This accounts for the few granules of degeneration in the nucleus cuneatus and in the external cuneate nucleus or Clarke-Monakow's nucleus. The degeneration

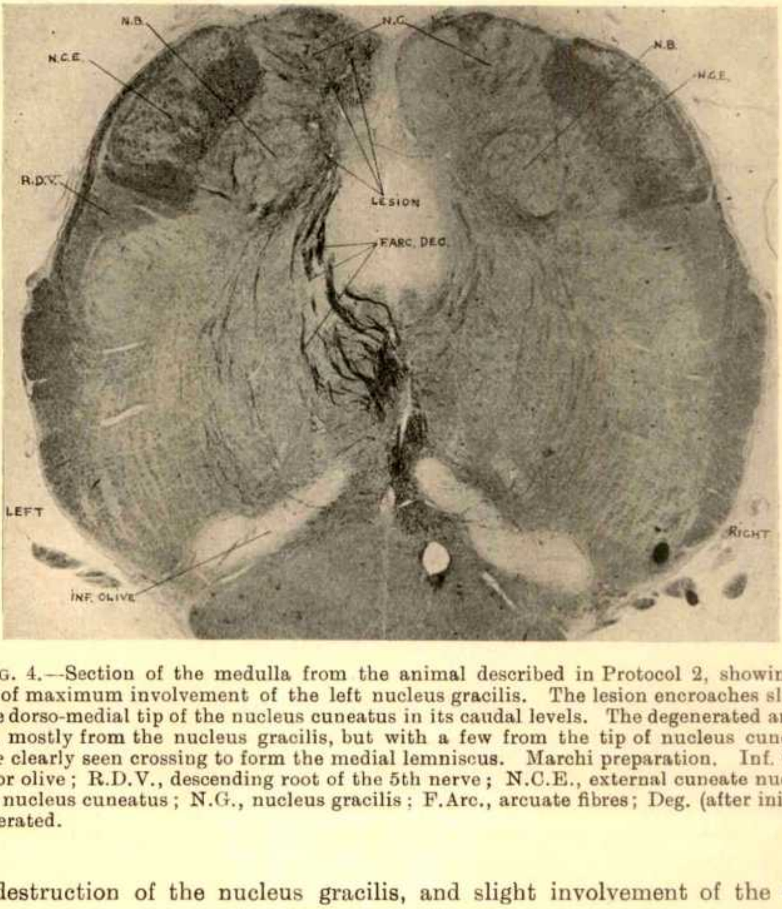

FIG. 4.—Section of the medulla from the animal described in Protocol 2, showing the point of maximum involvement of the left nucleus gracilis. The lesion encroaches slightly on the dorso-medial tip of the nucleus cuneatus in its caudal levels. The degenerated arcuate fibres, mostly from the nucleus gracilis, but with a few from the tip of nucleus cuneatus, can be clearly seen crossing to form the medial lemniscus. Marchi preparation. Inf. Olive, inferior olive; R.D.V., descending root of the 5th nerve; N.C.E., external cuneate nucleus; N.B., nucleus cuneatus; N.G., nucleus gracilis; F.Arc., arcuate fibres; Deg. (after initials), degenerated.

from the lesion of the nucleus gracilis could be followed frontally through the most medial of the internal arcuate fibres into the interolivary space and into the medial lemniscus. At the level of its greatest development the nucleus cuneatus is entirely free from damage. Fig. 5 shows the ascending degeneration in the medial lemniscus at a higher level. At lower levels the spinal cord contained no pyramidal degeneration.

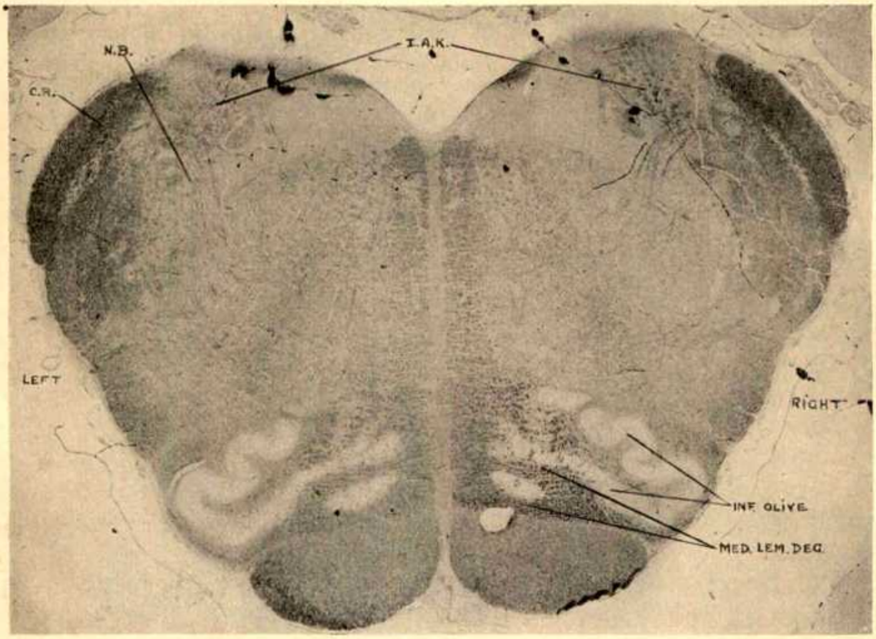

FIG. 5.—Section of the medulla from the same case as fig. 4 but at a higher level showing absence of involvement of the left nucleus cuneatus. The degeneration in the right medial lemniscus can be clearly seen. Marchi preparation. C.R., corpus restiforme; N.B., nucleus cuneatus; I.A.K., juxtarestiform bodies; Inf. Olive, inferior olive; Med. Lem., medial lemniscus; Deg. (after initials), degenerated.

Summary: A lesion limited to one nucleus gracilis was associated with symptoms confined practically entirely to the ipsilateral hind-limb. The slight temporary involvement of the arm may have resulted from slight injury of the most caudal portion of the nucleus cuneatus.

Protocol No. 3—*Cer.* 40.

Operation, January 25, 1934: *Lesion of the right nucleus cuneatus.*—While the animal was coming out of the anæsthetic there was a slight asymmetry owing to a flexion of the right fore-limb, but this disappeared rapidly as the anæsthesia wore off.

Three hours after operation.—With the animal well out of the anæsthetic there is very definite right-sided impairment, especially in the fore-limb. On movement the animal stumbles towards the right. It sits with the right side against the cage. There are no forced swaying movements such as are seen in vestibular animals. While sitting still the right fore-limb is slightly flexed at the elbow, the hand is in a normal position or slightly extended, and the arm is adducted. The right hand is not used in reaching for food, but the animal does this readily and accurately with the left arm. When the animal is teased with a stick it makes no attempt to grasp it with the right fore-limb. Reaching and grasping are performed quite well with the hind-limb. The right arm is used only slightly and in a clumsy manner for defence. The left arm is used normally. When the animal is taken out of the cage there is a slight abduction of the right hind-foot. In walking it relies little on the right fore-limb, and the hand is often placed with the dorsum downward and little attempt is made to correct this abnormal posture. The upper arm occasionally slips sideways when weight is placed upon it. The hand is generally carried as if it were an extra appendage. The right hand is occasionally clumsy, but it is not marked. Climbing is done chiefly with three limbs and the right hind-limb seems capable of grasping the cage fairly well. The right fore-limb makes poor attempts at grasping the cage and this limb is not employed in any finely co-ordinated movements. When the animal is suspended under a horizontal bar it climbs along fairly well, using the right hind-limb to some extent and seemingly capable of holding on to the bar with it, but the right fore-limb is used apparently only for support, the upper arm being turned around the bar. There is no abnormality in any of the cranial nerves. Muscles tone is definitely diminished in the right fore-limb at the shoulder, elbow and wrist. There is also slight diminution in tone in the right hind-limb as compared to the left, but this is not very marked, and is not so severe as in animals with lesions of the nucleus gracilis. So far as can be determined there is no diminution in the animal's responses to touch, deep pressure and pin-prick in any of the limbs, trunk or head. When blindfolded the animal allows a considerable change in position to be passively impressed on the right fore-limb without manifesting any resistance, in contrast to the left arm where strenuous resistance is shown to any change in posture. Movement of the right hind-limb elicits a quick defensive response. The deep reflexes in the upper arms and the knee-jerks are active and equal on the two sides. When the animal is dropped head first, there is slight extension of the right arm but not so marked as on the normal left side. The righting, position and other labyrinthine reflexes appear normal throughout. There is, however, a definite diminution in the placing and hopping reflexes in the right fore-limb. This is not so marked in the hind-limb.

January 26: *Twenty-four hours after the operation.*—The picture is essentially the same as on the previous day. However, the animal does not stumble in running as it did then, and the involvement of the hind-limb has cleared up considerably. The symptoms are mainly confined to the right fore-limb.

January 27: *Forty-eight hours after the operation.*—The condition was unchanged.

February 1: *One week after operation.*—The disturbances are confined to to the right fore-limb; they consist in lack of spontaneous use in grasping, diminution in appreciation of the sense of position, hypotonia, over-active deep reflexes and retained superficial sensory responses. The right hind-limb appears to be slightly involved, as it is clumsy in co-ordinated movements as in climbing along underneath a bar. A good grip is present and no diminution in tone is elicited in this limb. The right fore-limb is used occasionally in active movements, but in feeding it acts merely as a support, and is not employed in finer movements as grasping food. During the week the various vestibular tests have been found normal. The animal shows no abnormality in swimming.

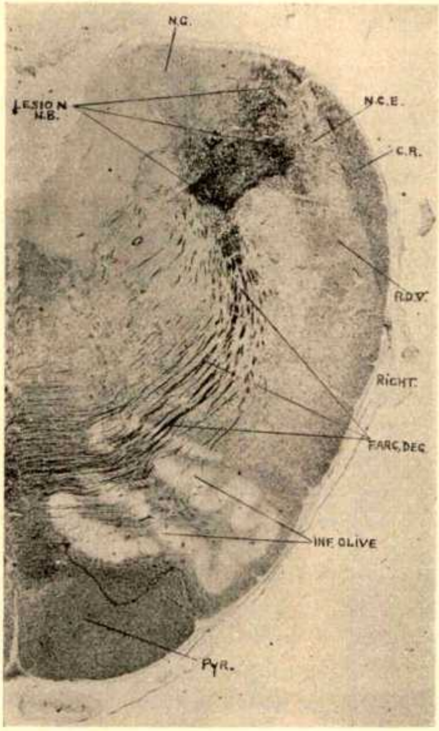

FIG. 6.—Section of the medulla from the animal described in Protocol No. 3 near the point of maximum involvement of the nucleus cuneatus. It shows involvement of the whole nucleus together with a small portion of the external cuneate nucleus (nucleus of Clarke-Monakow). The degenerated arcuate fibres from the right nucleus cuneatus can be seen bending ventrally to cross the midline to form the medial lemniscus of the opposite side. The restiform body is free from lesion. Marchi preparation. Pyr., pyramid; Inf. Olive, inferior olive: F. Arc., arcuate fibres; R.D.V., descending root of the 5th nerve; C.R., corpus restiforme; N.C.E., external cuneate nucleus; N.G., nucleus gracilis; N.B., nucleus cuneatus; Deg. (after initials), degenerated.

February 8: *Fourteen days after operation.*—The animal still presents essentially the same symptoms as were described in the previous week. It was killed on this date for study in serial Marchi preparations.

Anatomical Report.—The lesion was confined to the right side and involved essentially the nucleus cuneatus proper. It extended to the cephalic end of the funiculus cuneatus, where it involved part of the funiculus itself and the most caudal portion of the external cuneate nucleus (nucleus of Clarke-Monakow). At a slightly higher level the destruction involved mainly the nucleus cuneatus. There was, however, an injury of the most lateral fibres leaving the nucleus gracilis, and the lesion encroached laterally on the most dorso-medial portion of the external cuneate nucleus (Clarke-Monakow's nucleus) (fig. 6). At a slightly higher level the lesion was confined to the nucleus cuneatus. The degeneration of the arcuate fibres from the nucleus could be well seen. At a still higher level only the nucleus cuneatus was involved (fig. 7). This figure also shows the extensive degeneration in the opposite lemniscus. The restiform body on the side of the lesion contained a number of degenerated fibres, probably owing to the involvement of Clarke-Monakow's nucleus in the lower levels of the lesion. There was no evidence of injury of either the vestibular or of the pyramidal systems at any level.

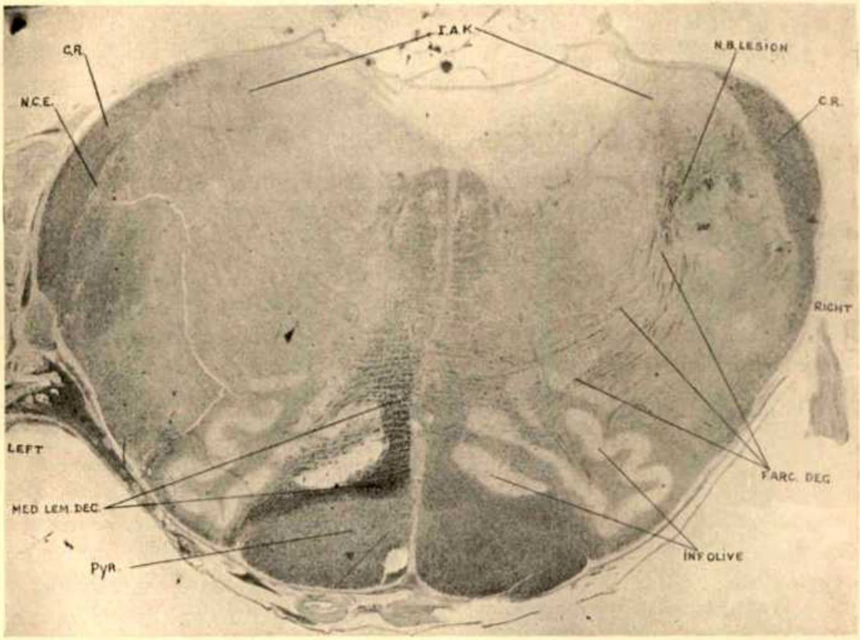

FIG. 7.—Section of the medulla from the same case as fig. 6, but near the upper end of the nucleus cuneatus which is alone involved. The degeneration in the left medial lemniscus and a few degenerated fibres in the right restiform body can be clearly seen. Marchi preparations. Pyr., Pyramid; Med. Lem., medial lemniscus; N.C.E., external cuneate nucleus; C.R., corpus restiforme; I.A.K., juxtarestiform bodies; N.B., nucleus cuneatus: F. Arc., arcuate fibres; Inf. Olive, inferior olive; Deg. (after initials), degenerated.

To summarize, we have a monkey with a lesion involving practically all of the right nucleus cuneatus in addition to a small proportion of the efferent fibres from the nucleus gracilis. Part of Clarke-Monakow's nucleus has also been injured. Some fibres of the funiculus cuneatus have undoubtedly been cut as they pass to through or around the nucleus cuneatus to the nucleus of Clarke-Monakow. Avoidance of this complication appears to be practically impossible owing to the anatomical relationships.

Protocol No. 4, *Cer.* 122.

Operation, September 13, 1933: *Bilateral lesions of both nuclei graciles and cuneati.* When the animal came out of the anæsthetic there was marked flaccidity of all limbs.

Three hours after operation.—With the animal well out of the anæsthetic a marked disability, such as is seen following complete cervical section of the dorsum columns, is present, with the difference however that the symptoms are more marked on the right side. The main symptom is failure to use the limbs for active grasping. For example, if one approaches the cage with a small stick the animal makes violent attempts to get away, but does not reach for the stick in defence except with the left fore-limb, with which it makes some movements but fails to grasp the stick accurately; it appears to be unable to flex the hands around the stick. The right limbs make no attempt at reaching. As the animal sits in the corner of the cage the arms are adducted to the side, the elbows are flexed, and the hands dangle apparently uselessly; the hind-limbs, and particularly the right, are abducted. Although very weak, when it is allowed to leave the cage the animal attempts to walk, but its feet tend to slip on the floor, all their movements are poorly co-ordinated, the feet are flung excessively upwards and outwards, and it occasionally falls to either side, or after a few steps it may lie down on the floor. There is no oscillation of its head, which is held straight. When it reaches a cage it attempts unsuccessfully to jump. It stretches towards a support with both hands, but the left hand alone seems capable of grasping; even then it lets go quickly and the animal is therefore unable to climb. When blindfolded the animal shows no active response to passive changing of the position of the limbs, except perhaps of the left fore-limb. The muscle tone is definitely diminished in all of the limbs, but more so in the right. The deep reflexes are over-active on both sides. The cranial nerves appear normal. The animal appreciates pin-prick, touch and deep pressure, as does the normal monkey. The placing and hopping reflexes are absent, except perhaps in the left fore-limb, where there is an occasional response. The animal can right itself from either side, and if dropped head first shows a slight extension of the fore-limbs, especially of the right.

September 14: *Twenty-four hours after operation.*—The same marked inability to use the limbs in co-ordinated spontaneous grasping movements is still present. It is absolutely unable to climb and to grasp the cage except occasionally with one or two fingers of the left fore-limb. Despite its inability to grasp the animal may, if hung from a high bar and dropped suddenly, grip the bar with both hands and hang securely for a period of fifteen to twenty seconds. The right side always relaxes first, however. The muscle tone, the deep reflexes and the special reflexes are unchanged. The disability in the hands is shown particularly when the animal attempts to eat; the right limbs are not employed, but the left hand may try, though without success, to pick up a peanut or a banana. The fingers are used clumsily and the grip is so insecure and poorly executed that the object is often dropped before it reaches the mouth. The lack of awareness of change of position in the limbs is unchanged. If the animal is placed across a bar or some support so that the arms hang free on one side and the feet on the other, it struggles to get off, but does not seem to be able to use the arms or feet to grasp the bar and lift itself from it. The sensory responses are unchanged. The gait still shows the marked excessive movements in the limbs, a rather wide base, slipping of the limbs, more particularly on the right, and the assumption of abnormal postures. When the animal sits its hind feet present a very broad base. Vestibular testing shows normal responses on both sides.

September 21: *One week after operation.*—The general physical condition of the animal is excellent. He presents, however, the same essential neurological findings as were present at the three-hour stage. During this week the animal has adopted a hopping type of gait such as was seen in our animal with cervical section of the dorsal columns, though the front limbs are used to a slightly greater extent than in the animals with the spinal lesion. There is still a lack of spontaneous grasping and inability to climb, to use the limbs in actual grasping, for defence, to bring food to the mouth, and to free it if it is placed across a bar. When the animal jumps it shows a very poor spring; there is apparently very little elasticity in the limbs, it lands heavily and the limbs slide on the floor. The sensory responses are normal throughout. The animal swims normally, and tests reveal no evidence of involvement of the vestibular apparatus.

September 24: *Eleven days after operation.*—The animal is in essentially the same state as at the earlier stage, although the symptoms are less pronounced. The chief abnormalities, including the staggering, the uncertain and inaccurate gait, the diminution in the spontaneous grasping, the hypotonia, the active deep reflexes and the loss of sense of position, are unchanged. These are more marked on the right side. The animal was killed on this date for examination by Marchi's method.

Anatomical report.—The lesion involves both nuclei graciles in their entire extent, and at its upper level it involves the whole right nucleus cuneatus. On the left a small part of the superior and outer part of this nucleus remains intact. On the left the external cuneate nucleus (nucleus of Clarke-Monakow) has been directly injured in its most dorsal quarter only. There are a few degenerated fibres in this nucleus due to involvement of the funiculus cuneatus before it enters the nucleus. On the right side the lesion extends directly into the external cuneatus nucleus (nucleus of Clarke-Monakow) in about its upper third. The internal arcuate fibres are completely degenerated on the right, but some of those from the uninjured upper and outer portion of the left nucleus cuneatus remain unaffected. The lesion itself has not involved the fibres of the I.A.K. or the restiform body on either side. At higher levels the degenerated arcuate fibres can be followed into the medial lemniscus, in which there is symmetrical degeneration on both sides. There is no evidence of degeneration of the vestibular tracts. Both restiform bodies contain degenerated fibres, which are more numerous on the right side. They presumably result from the involvement of the external cuneate nuclei, since no direct damage to the restiform body is evident. Sections below the lesion in the cervical, thoracic and lumbar segments show no degeneration in the pyramidal tracts. Fig. 8 illustrates the involvement of the higher portions of the nuclei graciles and cuneati and the resulting degeneration of internal arcuate fibres. On the right, the lesion is seen to be of greater extent, involving part of the nucleus of Clarke-Monakow. Fig. 9, at a higher level, shows the full extent of the degeneration in the medial lemniscus of each side.

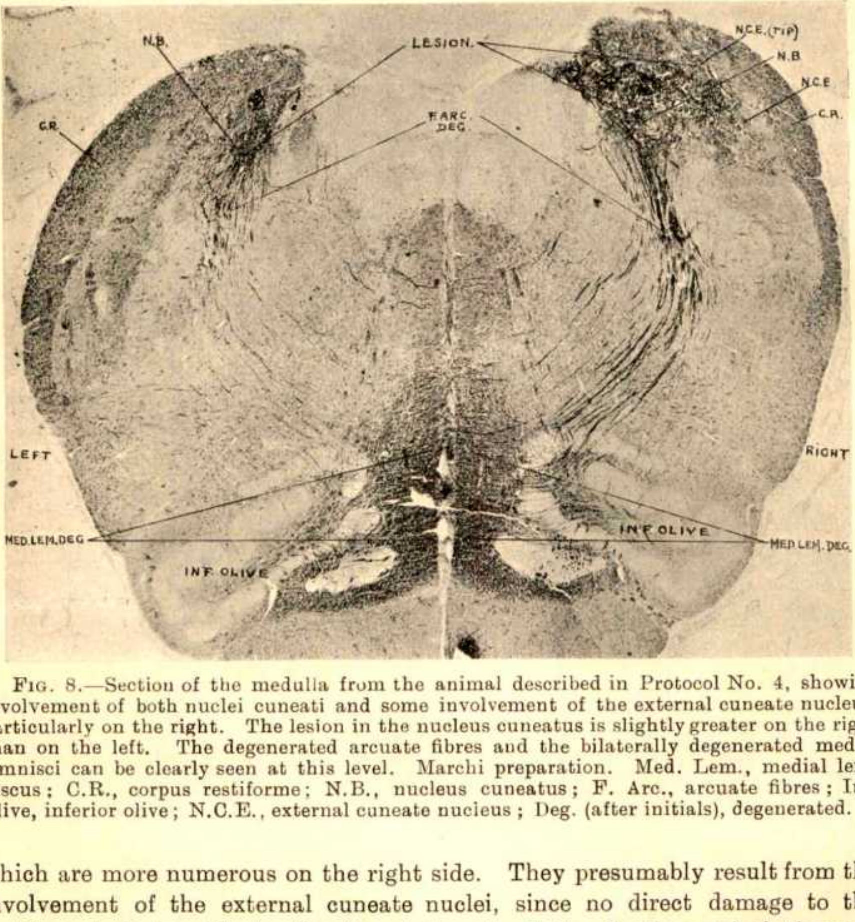

FIG. 8.—Section of the medulla from the animal described in Protocol No. 4, showing involvement of both nuclei cuneati and some involvement of the external cuneate nucleus, particularly on the right. The lesion in the nucleus cuneatus is slightly greater on the right than on the left. The degenerated arcuate fibres and the bilaterally degenerated medial lemnisci can be clearly seen at this level. Marchi preparation. Med. Lem., medial lemniscus; C.R., corpus restiforme; N.B., nucleus cuneatus; F. Arc., arcuate fibres; Inf. Olive, inferior olive; N.C.E., external cuneate nucleus; Deg. (after initials), degenerated.

In this animal the lesion involved the nuclei graciles and cuneati of both sides, but was larger on the right. On this side it extended into the external cuneate nucleus. There is degeneration of the medial lemniscus of both sides and a slight degeneration in the restiform bodies, especially on the right.

These four protocols are samples of typical cases from our large series of monkeys with different lesions of the dorsal column nuclei. In all cases the degeneration, especially when studied with the Marchi method, could be followed as far as the thalamic nuclei.

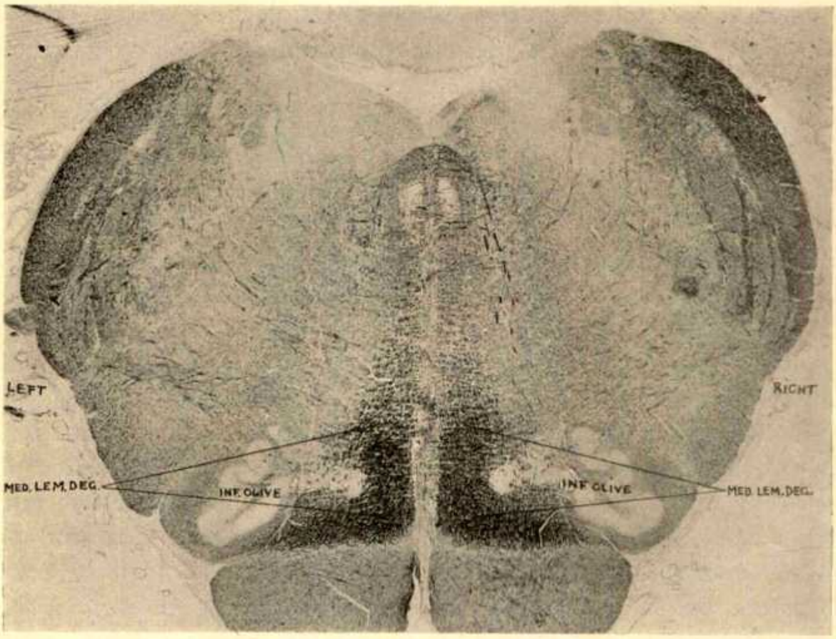

FIG. 9.—Section of the medulla from the same case as fig. 8, but at a higher level showing the bilateral symmetrical degeneration in the medial lemnisci. Marchi preparation. Med. Lem., medial lemniscus; Inf. Olive, inferior olive; Deg. (after initials), degenerated.

IV.—DISCUSSION.

In all of our animals with lesions of the dorsal column nuclei we were impressed by the similarity between their symptoms and those associated with lesions of the dorsal columns [1]. This is, of course, what one would expect, since the nuclei graciles and cuneati are the nuclei of the dorsal columns.

Zeehandelaar [10] concluded, as a result of his studies on the comparative anatomy of the dorsal column nuclei, that these nuclei are developed especially in higher animals, and that this development bears, in the main, a direct relationship to the increasingly independent use of the upper and lower limbs and the establishment of more cortical or conscious control. According to him the dorsal column nuclei are the intermediate stations for the long dorsal column fibres carrying impulses from the limbs, the impulses from the lower limb going to the nucleus gracilis, and those from the upper to the nucleus cuneatus, from which they pass by way of the medial lemniscus to the thalamus for redistribution to the cortex. He believes that there is probably a considerable mixing and redistribution of the fibres within the dorsal column nuclei. The external cuneate nucleus, or nucleus of Clarke-Monakow, according to this author, is related to the muscles of the neck.

Our work confirms the definite projection of the fibres from the lower limbs into the nucleus gracilis, and of the fibres from the upper limbs into the internal and external portions of the nucleus cuneatus. Since lesions of either of these nuclei produce symptoms in either the hind- or the fore-leg of the same side only, the distribution appears to be entirely ipsilateral.

In unilateral lesions of the nucleus gracilis the symptoms are confined to the ipsilateral hind leg, and consist mainly of inability to control the accurate placing of the limb and a diminution in the sense of position, associated with a certain degree of hypotonia and retention of the deep reflexes. The disturbances in the hind-limb are usually not so marked when the nucleus cuneatus is destroyed. This is due to the facts by which we have explained the severer symptoms in the fore-limb as a result of the section of the funiculus cuneatus. Our experiments on the dorsal columns and on the cerebellum have tended to show that the nucleus of Clarke-Monakow, or the external cuneate nucleus, receives a large number of fibres from the funiculus cuneatus and that it sends fibres to the cerebellum by way of the restiform body of the same side. This nucleus, therefore, forms an intermediate station between fibres of the funiculus cuneatus and the cerebellum ; it receives many of the impulses from the upper limb and neck muscles which ultimately go to the cerebellum. The medial cuneate nucleus or, as we choose to call it, the nucleus cuneatus proper, on the other hand, receives fibres from the funiculus cuneatus, and in turn sends arcuate fibres to the medial lemniscus and thalamus, carrying impulses which ultimately will be associated with conscious deep sensibility. We believe, as a result of our anatomical study of lesions in the funiculus gracilis [11], that the fibres from the lower extremities terminate in the nucleus gracilis, which sends its efferent fibres into the lemniscus. A lesion of the nucleus gracilis, therefore, involves no appreciable cerebellar connexion of the hind leg, and the disability resulting is dependent practically entirely upon a loss of the medullo-thalamic component. On the other hand, in lesions of the nucleus cuneatus, especially when the lesions extend far enough laterally to involve the nucleus of Clarke-Monakow directly, or the fibres from the funiculus cuneatus which pass into this nucleus, symptoms result not only from involvement of the fibres going to the contralateral cerebral cortex, but are also from loss of the impulses going to the ipsilateral cerebellum. The loss is noticeably greater when this is the case. This difference is exemplified very well in our Protocol No. 4, where the lesion on the right involved a greater portion of the external cuneate nucleus than it did on the left.

Our previous work [11] tended to show that there is a topographical projection from the funiculus cuneatus in Clarke-Monakow's nucleus. Its ventral end receives fibres from the upper two or three cervical segments, whereas its dorsal portion receives fibres from the lower cervical segments. It follows that a lesion extending into the ventral portion of Clarke-Monakow's nucleus would involve fibres from the upper cervical segments ending in it. On the other hand the involvement of the dorsal position of Clarke-Monakow's nucleus would involve fibres of the funiculus cuneatus coming from the lower cervical and upper thoracic segments.

In view of these facts it is easy to understand why lesions of the nuclei graciles and cuneati extending to the external cuneate nucleus, or nucleus of Clarke-Monakow, produce more severe symptoms than those limited to the nuclei graciles and cuneati, since the medullo-cerebellar fibres from the external cuneate nucleus are injured in addition to the medullo-thalamic fibres.

It is still an open question whether or not there is a greater predominance of fibres from the nucleus cuneatus or from the nucleus gracilis in the medial lemniscus. The dorsal column-cerebral component probably plays a greater rôle in the control of movements of the upper extremity than in those of the lower, since many of the movements of the lower extremity may be carried out on a spinal basis and therefore require less cortical control, or because the movements of the upper extremity in high forms, such as man and even the monkey, are a finer type and require more cortical control for successful execution. This may be the case. In order to check this experimentally, we have produced mid-line lesions of the medial lemniscus at the level of the inter-olivary space. By this operation the fibres of the lemniscus are divided at some distance from their nuclei of origin and surrounding structures, such as the funiculus cuneatus and the external cuneate nucleus, escape injury. We found then that the symptoms following section of the medial lemniscus were more marked in the fore-limb than in the hind-limb. This justifies the conclusion that the cerebral components are more important in the control of movements of the fore-limbs than in those of the hind-limbs.

It may be of interest here to mention the effects of removal of the post-central convolutions in animals in which there had been a previous lesion of the nuclei graciles and cuneati. In another paper, dealing with the effects of lesions of the post-central convolutions [12], we report symptoms which resemble very closely those seen following lesions of the dorsal column nuclei. These are essentially a marked difficulty in performing co-ordinated movements with the limbs, associated with a deficiency in the sense of position. The symptoms here also were greater in the fore- than in the hind-legs. In one of our animals in which the gracile and cuneate nuclei had been destroyed on one side, the contralateral post-central convolution was removed after the animal had reached the chronic stage, when further improvement had ceased. In this animal the subsequent removal of the post-central contralateral convolution added nothing to the symptoms. In another animal in which both nuclei graciles and cuneati had been removed and in which the animal had likewise reached a chronic stage, subsequent removal of both post-central convolutions lead to a temporary return of the symptoms which had been observed immediately after the first operation.

It is probable that the lesions in many of our animals were more strictly confined to the dorsal column nuclei than in some of the experiments reported by various authors; this may account for our failure to obtain symptoms described by them. For example, our animals had no degeneration in the pyramidal tracts and no direct involvement of the spino-cerebellar system or restiform body. We have not observed the retropulsion or forced falling to one side which were described by Bechterew and by Ferrier and Turner. Bechterew concluded that the main symptom was a disturbance in equilibrium, but if by this something akin to a vestibular disturbance of equilibrium is meant, it cannot have been due to lesions of the dorsal column nuclei, for our animals in which there was no evidence of vestibular damage showed no tendency to rolling or forced lateropulsion.

Our findings tend to confirm our observations on monkeys with section of the dorsal column where no evidence of loss of sensibility to pain, touch or deep pressure was found. They also confirm the exaggeration of the deep reflexes and of hypotonia after lesions of the dorsal columns. The hypotonia is not entirely due to involvement of the medullo-thalamic fibres, although it occurs with lesions of the lemniscus and of the post-central convolution. It is, however, much greater when the cerebellar components are also injured.

As yet we have not been able to produce lesions confined to the external cuneate nucleus (nucleus of Clarke-Monakow), although in one case, where alcohol injected into this nucleus with a fine needle damaged its dorsal portion only, the symptoms resembled those of a partial lesion of the ipsilateral restiform body and they were not associated with any loss of sense of position in the ipsilateral fore-limb.

It is not our intention to insist that the entire cerebellar component from the upper limb passes to the cerebellum by way of the external cuneate nucleus, in fact our experiments show that there is a cerebellar component from the upper limb in the dorsal spino-cerebellar tract, and monkeys in which lesions confined to the dorsal spino-cerebellar tract were made at the third cervical segment presented in the fore-limb symptoms typical of damage of the ipsilateral restiform body. The pathway through Clarke-Monakow's nucleus is therefore probably only one of the existing pathways, but the large number of fibres from the cervical dorsal columns which enter the nucleus indicates that it may be a pathway of considerable importance.

V.—CONCLUSIONS.

(1) Following lesions of the nuclei graciles and cuneati in macacus rhesus monkeys the symptoms which occur are mainly a loss of sense of position in all extremities, hypotonia and a transient loss or diminution of the hopping and placing reflexes. There are no appreciable changes in superficial sensibility, and the deep reflexes are not only preserved but appear to be increased.

(2) If the lesion involves exclusively the nucleus gracilis, these symptoms are limited to both hind legs if the lesion is bilateral, and to the ipsilateral leg if the lesion is unilateral.

(3) If the lesion is restricted to the nucleus cuneatus (internal cuneate nucleus) the symptoms are limited to the upper extremities if the lesion is bilateral, or to the ipsilateral extremity if the lesion is unilateral.

(4) The disturbances in the upper extremities resulting from lesions of the nuclei cuneati are more pronounced than those in the lower extremities following lesions of the nuclei graciles. This is partly due to the fact that in producing complete destruction of the nucleus cuneatus a certain number of fibres of the posterior columns to the cerebellum via the external cuneate nucleus (Clarke-Monakow's nucleus) are generally destroyed.

(5) When the lesions of the posterior column nuclei involve also the external cuneate nucleus (Clarke-Monakow's nucleus) which represents a relay station from the posterior column of the cervical segments to the cerebellum, the symptoms are more pronounced because of the involvement of the cerebellar component.

(6) The symptoms resulting from the lesions of the nuclei graciles et cuneati are similar to those following destruction of the posterior columns at high cervical levels. The intensity of the symptoms is not, however, quite as pronounced as when the posterior columns are completely destroyed. This is due to the fact that in the lesions of the posterior columns at the cervical level their cerebellar component which passes through the external cuneate nucleus (Clarke-Monakow's nucleus) is also destroyed.

(7) The symptoms of lesions of the nuclei graciles et cuneati are similar to those which follow removal of the post-central convolutions, but the latter are less pronounced since the medial lemniscus sends impulses not only to the post-central, but also to the pre-central and parietal cortex.

BIBLIOGRAPHY.

[1] Ferraro, A., and Barrera, S. E. "The Effects of Lesions of the Posterior Columns in Macacus Rhesus Monkeys," *Brain*, 1934, **57**, 307.

[2] *Idem.* "The Effects of Lesions of the Dorsal Spino-cerebellar Tract and Corpus Restiforme in the Macacus Rhesus Monkey," *Ibid.*, 1935, **58**, 174.

[3] Bechterew, W. "Ueber die Erscheinungen welche die Durchschneidung der Hinterstränge des Rückenmarkes bei Thieren herbeifuhrt uber die Beziehungen dieser Strange zur Gleichgewichtsfunction," *Arch. f. Anat. und Physio. Physiologische Abt.*, 1890, 489.

[4] Ferrier, D., and Turner, W. A. "A Record of Experiments Illustrative of the Symptomatology and Degenerations following Lesions of the Cerebellum and its Peduncles and Related Structures in Monkeys," *Proc. Roy. Soc. of London*, 1893, **54**, 476.

[5] Mott, F. W. "Experimental Enquiry upon the Afferent Tracts of the Central Nervous System of the Monkey," *Brain*, 1895, **18**, 1.

[6] Turner, W. A. "The Results of Experimental Destruction of the Tubercle of Rolando," *Ibid.*, 1895, **18**, 281.

[7] Tschermak, A. "Ueber den centralen Verlauf der aufsteigenden Hinterstrangbahnen und deren Beziehungen zu den Bahnen im Vorderseitenstrang," *Arch. f. Anat. u. Physiol. Anatomische Abt.*, 1898, 291.

[8] Probst, M. "Zur Anatomie und Physiologie des Kleinhirns," *Arch. f. Psychiat.*, 1902, **35**, 692.

[9] Mussen, A. T. "Experimental Investigations on the Cerebellum," *Brain*, 1927, **50**, 313.

[10] Zeehandelaar, I. "Ontogenese und Phylogenese der Hinterstrangkerne in Verband mit der Sensibilität," *Folia neurobiologica*, 1921-22, **12**, 1.

[11] Ferraro, A., and Barrera, S. E. "Posterior Column Fibres and Their Termination in the Posterior Column Nuclei." In press for publication in the *Journ. of Comp. Neurol.*

[12] *Idem.* "The Effects of Removal of the Post-central Convolutions in the Macacus Rhesus Monkey." In preparation.

FAMILIAL SCHILDER'S DISEASE.

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In spite of the number of valuable publications concerning Schilder's disease and especially its familial variety, many problems remain unsolved. This is clearly shown by L. Bouman [8] in his recent monograph which deals with the current pathogenetic and nosological aspects of the disease. It is hoped to contribute some points that may justify the following report of a family suffering from this condition, observed and investigated by us in the Maudsley Hospital and in the Central Pathological Laboratory.

Case 1.—F. H., boy aged 9. First seen June 4, 1928, complaining of increasing deafness of three months' duration. He had been a full-time child; delivery was normal; he walked and talked at one year; he had an epileptiform fit about the age of 2; went to school at the age of 4 and was considered to be quite bright. At the age of 6 years he had a severe attack of jaundice which lasted two weeks, during which he was said to have been seriously ill. Since then he has suffered from bilious attacks and diarrhœa. Three months ago he was noticed to be somewhat deaf. This was attributed to a fall from a swing, his head having caught something in the fall. Thereafter he became dull and inattentive at school and was considered lazy. His deafness has varied, at times it was complete.

On examination he was rather apathetic, but otherwise his behaviour was normal. Vision was impaired, the pupils reacted sluggishly to light and on accommodation, the fundi were normal. There was marked deafness, and ataxia and inco-ordination of his left arm and left leg. The reflexes of arms were sluggish, those of legs were brisk. The abdominal reflexes were active and equal—the plantar reflexes were both flexor. Six months later he was more apathetic, irritable, at times noisy, screaming loudly and whining. Deafness was practically complete and visual impairment more marked. There was pallor of the optic discs, but not sufficient to account for degree of visual impairment. The ataxia was greater and he had developed a marked cerebellar posture. The deep reflexes of the arms were sluggish, those of the legs were brisk. The abdominal reflexes remained active, but both plantars were extensor in type. Wassermann reaction was negative in blood and cerebrospinal fluid. The latter contained cells 4 per c.mm.; protein 80 mg. per cent., and gave a Lange curve 5554432100 (repeated and confirmed).

The illness ran a protracted course; by June, 1929, he was able to move in bed from side to side but unable to raise himself. He opened his mouth when his lips were touched and could swallow without apparent difficulty. He was noisy when moved and had frequent attacks of screaming. He was completely deaf and totally blind. The pupils were dilated and inactive and both optic discs showed marked atrophy. The limbs were spastic; all the deep reflexes were exaggerated. The abdominal reflexes were absent and both plantars were extensor in type. He went downhill gradually, swallowing became increasingly difficult and he died on July 15, 1929.

Post-mortem findings.—The body was emaciated. No marked changes were found in the visceral organs, which were small. There is no record of marked changes on macroscopic examination of the brain, which was hardened before section.

Pathological examination.—In horizontal sections the changes are seen to begin in the central portion of the white matter of the frontal lobe and to increase gradually, reaching a maximum extent in the parietal, temporal and occipital lobes. Here the white matter has completely disappeared. Within the affected area the formalin-hardened tissue is of a grey colour and of a peculiar elastic and tough rubber-like consistency. Weigert-Pal sections confirm the naked-eye appearance, and, in particular, show more or less complete demyelination in the posterior two-thirds of the white matter of both hemispheres. Except for a slight rarification, the myelin architecture of the cortex is intact throughout. The sub-cortical fibres generally, but not invariably, stand out against the demyelinated part of the white matter.

The basal ganglia are free from gross changes, whereas there is complete demyelination in the pyramidal and occipito-temporo-pontine tracts. The fronto-pontine tracts are better preserved. The destruction of the pyramidal tracts can be traced throughout the pons and medulla oblongata to the spinal cord, which, like the cerebellum, is otherwise free from change.

Within the demyelinized regions the disappearance of axis-cylinders in the Bielschowsky picture corresponds closely to that of the myelin sheaths. Only at the margin of the process, towards the unaffected part of the frontal lobe, is the preservation of axis cylinders greater than that of the myelin sheaths. Here the demyelination begins with a gradual patchy failure to take up the myelin stain, and offers no sharp line of demarcation. Throughout the affected areas of the white matter much fibrous glial proliferation is found, as shown by the Holzer stain. This proliferation is denser in the vicinity of the arcuate fibres than in the centre, where it is of a spongy structure.

Cell pictures (cresyl-violet, hæmatoxylin-eosin, Heidenhain, azocarmine, special glial stains) show that the cyto-architectonic structure of the cortex has not suffered considerably except for some glial proliferation immediately beneath the pia mater and in the deepest layer adjacent to the white matter. In the marginal part of the process, near the arcuate fibres and the normal frontal lobe, there is a considerable "wall" formation, consisting of multinucleated plump cells, large and small granular compound cells, proliferated astrocytes and microglial cells. The plump cells appear to be the earliest sign of the process. The oligodendroglia is not appreciably affected in the demarcation zone, no mucocytic material being found. The nearer one proceeds to the centre of the process the more do granular compound cells decrease in number. The prevailing cell here is the plump cell which is found with almost monotonous regularity (fig. 1). Granular compound cells in larger quantities are confined to the vessel sheaths. Micro- and oligodendroglia are, in contrast to the marginal zone, definitely diminished in the centre of the process. There is throughout the demyelinated area a considerable amount of inflammatory reaction made up of lymphocytes and plasma cells which penetrate very frequently the glial membrane and lie free in the parenchyma. Many of the granular compound cells round the vessels contain yellowish green pigment (with cresyl-violet), giving a marked iron reaction. This is never found in the cortex. No inflammatory changes of any marked degree occur outside the affected area.

With Scharlach-R stain one is struck by the excessive amount of "neutral" fat in many of the phagocytic and endothelial cells of the marginal parts. As the centre of the process is approached, this bright red colour is encountered only in a few endothelial and granular compound cells around the vessels. Here most of the lipoid remains in the "prelipoid" stage. The plump cells, both at the margin and at the centre, either contain no fat, or show only a few brick-coloured granules in the periphery of the cell bodies and their processes. These granules are also demonstrable sometimes with iron hæmatoxylin, Bielschowsky's and azocarmine stain. In general, however, these staining methods do not reveal more of these substances than the Scharlach-R method, unlike the case recorded by van Bogaert and Scholz [7]. Many of the prelipoid inclusions resist solution after treatment for forty-eight hours in acetone, pyridine, xylol, ether, chloroform, ethylalcohol, methyl-alcohol, hydrochloric-acid-alcohol or mixtures of these fat solvents, whilst all the bright coloured substances are readily dissolved. Exposure to heat at 50° has no apparent affect on the prelipoids. The result of the histochemical treatment corresponds in some degree to that obtained by Schlesinger, Greenfield and Stern [31] in a case of late infantile amaurotic idiocy. No prelipoid substances are found in the unaffected frontal lobe.

The histological investigation of the organs is not very fruitful. There is a moderate degree of fatty degeneration in the cells of the liver and the tubules of the kidney. The spleen, pituitary, suprarenals, pancreas, thyroid, parathyroid and the lymphatic glands appear normal. The testicle is immature and contains a small well-defined tumour-like focus, consisting of epithelial cells. All the fatty substances in the organs are of the common neutral fat character and dissolve readily in the normal fat solvents. No prelipoids are encountered.

Case 2.—D. H., a boy aged 4, was brought for examination by his mother, on March 21, 1929, as she considered that he was becoming like his elder brother. He complained of severe headaches, sickness, vomiting and diarrhœa—was definitely jaundiced during the past ten days. He was unsteady on his feet and tended to fall frequently. His left pupil was larger than the right, but they reacted normally. No other abnormal signs were made out on neurological examination. His gastro-intestinal trouble cleared up within seven days. Level of general intelligence was normal. He remained under observation. Although he was unsteady on his feet and appeared to drag his left leg no definite weakness was made out. In December 1931 he was admitted to hospital. His general condition was poor. His gait was unsteady and he threw out his legs with wide base. There were extensive septic abrasions on each knee owing to frequent falls. Romberg's sign was negative; the sense of position was good. No abnormality of sensation was detected. Speech was somewhat slurred. The pupils were unequal, but reacted normally; the fundi were normal. Hearing was not impaired. The deep reflexes of arms and legs were active, the abdominal reflexes were active, and both plantars were flexor in type. The Wassermann reaction was negative in the blood and cerebrospinal fluid. The latter contained cells 3 per c.mm., protein 15 mg. per cent.; the Lange reaction was negative. Throughout 1932 he complained of periodic attacks of severe headache accompanied by sickness and vomiting.

The following year his symptoms became rapidly more severe. In May 1933 his hearing was less acute and he had difficulty in seeing. By September considerable deterioration had developed; he was quite deaf and totally blind, the pupils were large, equal and inactive, and his optic discs showed atrophy. His speech was slurred, his talk was at times an unintelligible jargon. At other times one could make out quite easily what he said. The cerebrospinal fluid was re-examined; the Wassermann reaction was negative, the cells were 5 per c.mm., and protein 80 mg. The Lange test gave 1243210000. Three months later he was confined to bed, the condition was progressing rapidly. He sat in a characteristic pose, head held at an angle, occiput to the left and chin pointed to the right. The degree of pallor of optic discs had increased. His legs were spastic and the deep reflexes of the limbs were exaggerated. The abdominal reflexes were absent and both plantar reflexes were extensor in type. He was frequently noisy, resisted attention, feeding was difficult and he had difficulty in swallowing. He was frequently incontinent of urine. On January 5, 1934, he developed a twitching of the right side of his mouth and face which extended to eyelids and then to left arm and leg. He had continued seizures for a period of six hours, did not regain consciousness, and died the following day.

Post-mortem findings.—No gross changes were visible in the visceral organs, except a few patches of fatty change in the liver and encapsulated old tuberculous foci in the right lung. The brain weighed 1,410 grms. No macroscopic changes are on record. It was hardened before section.

Pathological examination.—After hardening in formalin coronal sections were made throughout the brain. The involvement of the white matter is strikingly similar to that of the first case in that the frontal lobe is preserved as a whole, while extending backwards the changes increase rapidly until they involve all the white matter. As in the first case, the process is nearly symmetrical. The consistency is much softer and is of a gelatinous character. The arcuate fibres are usually well preserved. The corpus callosum is less affected than the rest of the white matter. Immediately in front of the anterior part of the process is an œdema which also involves the cortex.

Myelin sections show in general the same extent of degeneration as Case No. 1, except that here there is also a demyelination of the fronto-pontine tracts and the pyramidal tracts are involved to a minor degree. The changes in the chiasma and the optic tracts will be considered later.

As to histological detail we only mention that there is a demyelination with corresponding destruction of the axis-cylinders similar to that found in Case 1. In the affected areas the infiltration of the vessels with plasma cells and lymphocytes penetrating into the parenchyma, is still more pronounced (fig. 2). No iron is found in the cells of the vessels. In the demarcation zone, near the arcuate fibres and the frontal lobe, the degeneration of the myelin appears to be more intense than in the first case and the microglial proliferation is greater. Corresponding to the zone of œdema there is a considerable degree of swelling of the oligodendroglia, but no mucocytic material is formed. Again the first signs of the process are plump cells. Sometimes one gains the impression that the oligodendroglia participates in the formation of granular compound cells. In the centre of the process oligodendro- and micro-glia are again markedly diminished. Plump cells, so predominant a feature in the first case, are here only rarely seen. Between the much looser fibrous glial network formed by ordinary astrocytes, large masses of granular compound cells are found (fig. 2). Scharlach-R stain reveals, not only in the marginal part but also in the centre, much brighter coloured lipoidal material which can be washed out nearly completely by all the fat solvents previously mentioned. Even those lipoids showing the pink colour readily dissolve. Plump cells do not participate in the uptake of lipoids. Some of the prelipoid substances are stainable by iron hæmatoxylin and ammoniacal silver. The frontal lobe is histologically normal. The cortex shows only a slight diffuse thickening of the covering glial layer; in the deepest layers adjacent to the process, changes occur in the ganglion cells and proliferation of the glia is to be noted.

Histological examination of the visceral organs does not reveal any changes worthy of note.

Case 3.—E. H. (Mrs.), aged 37, attended hospital April 14, 1934, complaining of general weakness, loss of interest and ataxia. She dated the onset of her symptoms to four months previously, though she had been working, as a cleaner, until two weeks ago. Her previous health had been good, without history of serious illnesses. She has been married sixteen years; was unhappy, as her husband was alcoholic and frequently abused her. They separated four years ago. There had been four children by this marriage. She has had a fifth since she separated from husband who denies paternity:—

(1) Frank, died aged 10—Case 1.

(2) Edgar, aged 13. General condition not good, frequent diarrhœa, con-

PLATE I

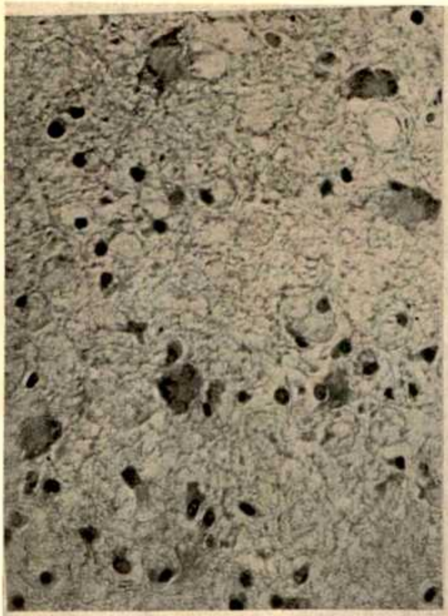


Fig. 1

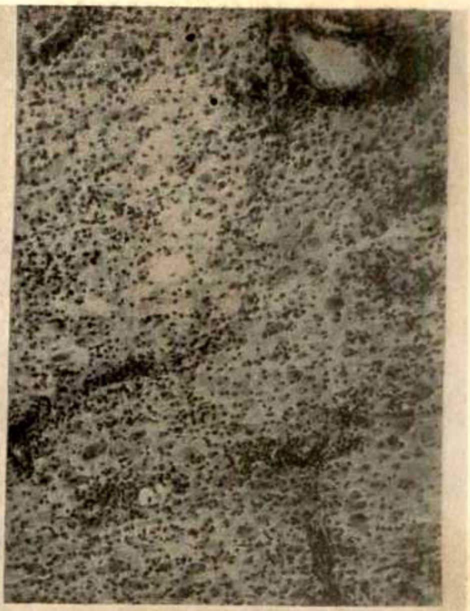
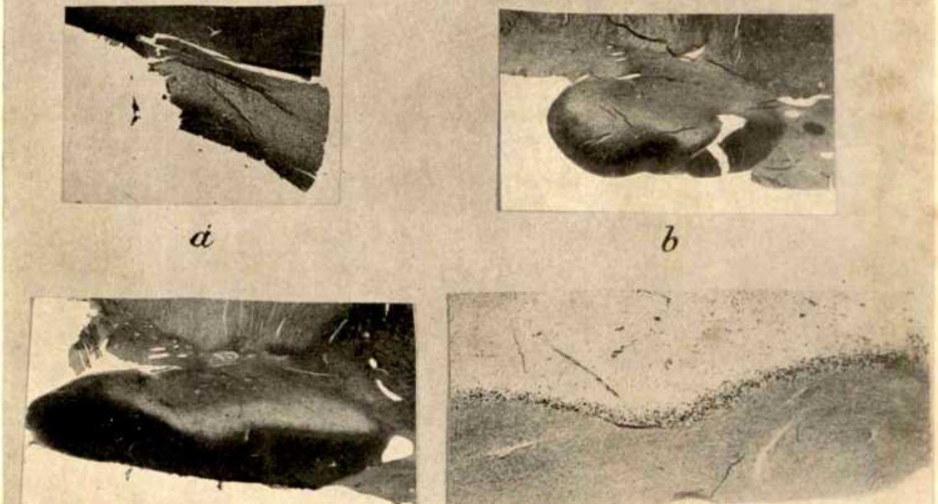


Fig. 2



a

b

c

d

Fig. 4

To illustrate paper by Alfred Meyer and Thos. Tennent.

sidered to be unsteady on feet and to "fall about." Never without septic abrasions on knees and legs. Neurological examination completely negative

(3) Stanley, aged 11. General health poor, said to have gastro-intestinal trouble, otherwise nil abnormal.

(4) Dennis, died aged 9. Case 2.

(5) Peter, aged 4, enjoys good health; is in a residential school.

Family history: It has been possible to obtain particulars of four generations of both the patient and her husband. These are tabulated in fig. 3. Chronic alcoholism is prominent on both sides. There is no history of nervous illness, nor is there any record of an illness, the course of which seemed obscure, or like that of any of the patients here recorded.

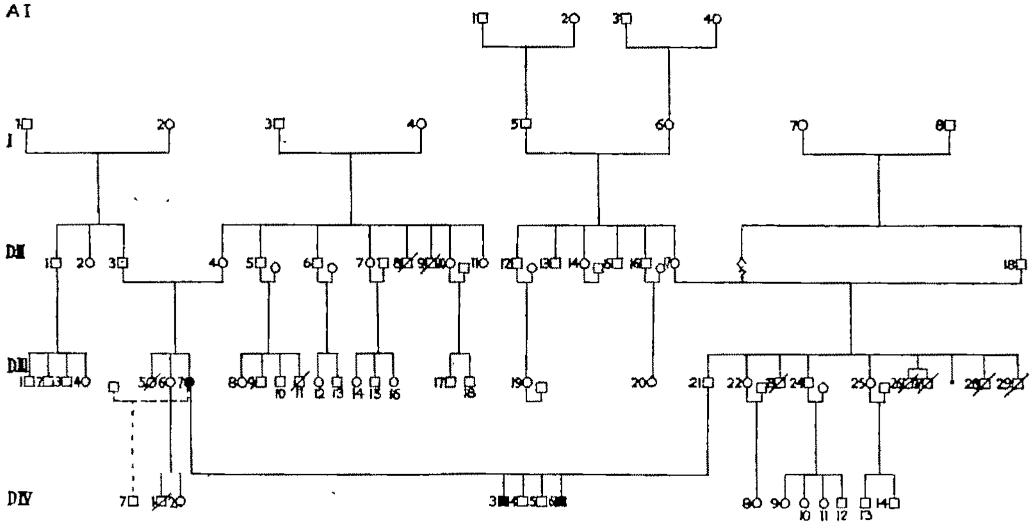


FIG. 3.

On examination she was apprehensive, emotionally unstable and convinced she was becoming like her two children who had died in hospital. She complained of mistiness of vision. Her visual acuity was R. $\frac{6}{6}$, L. $\frac{6}{9}$; there was no impairment in her visual fields. The fundi were normal. Hearing in her left ear was somewhat impaired. She complained of ataxia. With eyes closed and feet together she swayed considerably but maintained her balance. She was unable to walk along a line on the floor. Sensibility to touch and pinprick was more acute on the right side of the body. Vibration sense was lost on the left leg but present on the right. There was no astereognosis. The deep reflexes of the arms were equal and active, those of the right leg were more active than those of the left. Upper abdominal reflexes were active, the lower were absent. The left plantar reflex was extensor in type, the right gave a doubtful response. The Wassermann reaction was negative in the blood and cerebrospinal fluid. The fluid contained cells 2 c.mm., and protein

30 mg. per cent. Lange's reaction was negative. Gastric test meal shows slight diminution in acidity, well within normal limits. Blood-count: R.B.Cs. 4,520,000; W.B.Cs. 4,700; Hb. 10·4 grm. per cent.; C.I. 0·8; blood cholesterol 90 mg. per cent.

Since then her condition has progressed slowly. Giddiness troubled her and she has injured herself by falling. Headaches associated with vomiting were troublesome. She has developed incontinence of urine. There is hyperæsthesia to touch over the whole of the left side of her body. Vibration sense on the upper limbs is intact, but is lost over both lower extremities. She fails to recognize figures written on the skin of her legs but does so quite easily over her arms. The degree of ataxia has increased and Romberg's sign is positive. There is marked hyperflexion in walking. No definite paresis is present. The pupils are equal and react briskly to light and on accommodation. The temporal sides of both discs are somewhat pale; the visual fields are normal. The ocular movements are normal and there is no nystagmus. Some degree of deafness has developed in the left ear but cranial nerves are otherwise normal. The deep reflexes of upper limbs are active and appear equal; those of lower limbs are exaggerated, greater on the right leg. There is a right ankle clonus. The abdominal reflexes are absent. Both plantar reflexes are extensor in type.

The discussion can be limited with advantage to a few of the most important features.

The familial character of our cases is obvious. It is interesting to note that the mother's illness did not manifest itself before the onset of the disease in her children. A clear diagnosis of her condition is not yet possible. There are symptoms suggestive of a condition like disseminated sclerosis rather than spastic spinal paralysis. Early subacute combined degeneration has also been considered. As to the diagnostic evaluation of the condition occurring in members of earlier generations, it is well to remember that pathological evidence on this point is, as far as we can see, not yet on record.

It is striking to note the recent rapid increase in the number of familial cases since Krabbe [23], and particularly Scholz [34], drew attention to their occurrence. Since then one of Collier and Greenfield's [12] sporadic cases has proved to be familial, and the same applies, as we shall show in a later communication, to the first case of Stewart, Greenfield and Blandy [37]. It may well be that the familial group will play a much more dominant role in future classification.

From the pathological point of view the similarity in distribution is very striking in the two cases examined. It shows itself not only in the preservation of corresponding parts of the frontal lobes, but also in preservation of the basal ganglia, cerebellum, and even, as we will see later, in minor characteristics, such as lesions of the chiasma and optic tracts. This similarity of distribution may be determined by a constitutional factor. It must be mentioned, however, that the pathological changes found in familial cases do not always correspond so clearly, as exemplified by cases in the literature and our own further observations, not yet published.

The intensity of inflammation and the presence of inflammatory cells outside the vessel sheaths seems to surpass what has been found previously in familial cases. It may still be called "symptomatic," particularly if one considers that the tendency of a secondary inflammatory response to the decomposition of myelin is greater than usual (Cheng Yü Lin) [11]. It exemplifies, however, the difficulties of a classification based on the presence or absence of inflammatory changes, which is still believed, at least in some quarters, to be valid. The deep-rooted tendency to base classification on more or less superficial single histological features, is losing more and more ground (Spielmeyer [36], Bielschowsky and Maas [3], Guttmann and Bodechtel) [4, 5]. This applies not only to inflammation, but also to Bielschowsky's and Henneberg's [2] criterion, that in the "inflammatory" group the total demyelination originates from separate coalescing foci. We have seen this form of growth in another familial case which will be described in a later communication. It may even apply to the prelipoid substances which Scholz believes to be a feature of the heredo-degenerative cases only. Perhaps they have been found prevailingly in familial cases because they have there been specially searched for. The insufficiency of a histological classification is still more obvious if one takes into account the possibility of an extracerebral pathogenic mechanism. Take the example of pernicious anæmia. Here, Strauss, Heath and Castle [38] have advanced the view that the pathological changes in the blood and in the cerebrospinal system result from the lack of a factor normally present, the disappearance of which may be caused by an intrinsic abnormal function of the liver and the mucosa of the stomach, or by an extrinsic nutritional deficiency. According to this view, whatever the difference in the origin, the final attack on the central nervous system will be the same. We do not want to associate pernicious anæmia too closely with the processes included under the heading of "Schilder's disease"; it is not inconceivable that in the latter an extracerebral factor may be originally at work. (Ferraro [15], Macnamara and Dickson [26], *et al.*).

Greenfield [19] recently had something similar in view when he suggested that his cases of infantile progressive sclerosis were supplied with abnormal lipoids. It is in the light of such or similar conceptions that gastro-intestinal troubles at the onset of symptoms, in a group of Schilder's disease, become important. Globus [18] considers an onset with gastro-intestinal troubles as characteristic of many cases of Schilder's disease. Gastro-intestinal disturbances preceded not only the neurological symptoms of the two cases described here, but they are also recorded in the history of two of the other children, only one of whom shows as yet nervous symptoms (slight degree of ataxia). The interval between the gastro-intestinal attack and the manifestation of neurological symptoms in our two cases is very long (the mother suggests that the children never fully recovered from the attack of jaundice).

The consideration of a possible extracerebral pathogenic factor makes careful examination of the bodily organs indispensable. Moreover, the formation of prelipoid substances in cases of Schilder's disease has suggested comparison with amaurotic idiocy, which is, as shown by Bielschowsky and others, often associated with the changes in the viscera, known as Niemann-Pick disease. The appearance of prelipoid material in otherwise intact areas of the brain in cases of Schilder's disease (Bielschowsky and Henneberg) [2], the enlargement of liver and spleen in Kaltenbach's [22] case and the metachromatic substances found by Witte [40] in the visceral organs, seem to point in the direction of a more generalized disturbance. Histological examination of the viscera of familial cases of Schilder's disease has, however, been somewhat neglected. The result in our cases was negative; changes seen do not differ from those commonly found in the terminal stages of other conditions. There are no prelipoid substances comparable to those found in Niemann-Pick disease, and in xanthomatosis which might be connected also with lesions of the white matter (Davison) [13]. Unfortunately, we were not able to examine histologically the gastro-intestinal tract of our cases.

The presence of prelipoid substances has been used by Scholz [33, 34], who discovered them first, as the basis of his theory of primary glial insufficiency, which has found much favour (Bielschowsky and Henneberg [2], van Bogaert and Bertrand [6] and others). It is interesting, however, to note that our second case, with its more rapid course both clinically and pathologically, showed a greater activity of the microglia in the formation of ordinary scavenger cells than our first case, which resembles more closely that recorded by van Bogaert and Scholz [7]. Correspondingly, the breakdown of degenerated myelin to neutral fat is in the second case much more complete than in the first, as seen, for example, from the reaction of the lipoids towards fiat solvents. That is only a single observation, but in the light of other views regarding Scholz's interpretation (Bodechtel and Guttmann [4, 5], Patrassi [29], Hallervorden and Spatz [20], Bouman [8]) it may become more significant. Cases like those described by Ferraro [14], which combine a mild and protracted clinical course with extreme passivity of the glia and the most incomplete elaboration of the destroyed myelin, emphasize the difficulties of interpretation. Passivity of the glia does not necessarily mean insufficiency, and, according to Patrassi [29], the prelipoid substances can also be accounted for by a primarily abnormal character of the myelin products of disintegration.

Another group of writers suggests as the cause of the process a primary attack on the oligodendroglia (Hortega [21], Bailey and Schaltenbrand [1], Collier and Greenfield [12], Levaditi [24, 25] and others). Greenfield [19] gave recently an impressive example of mucocytic degeneration of the oligodendroglia connected with demyelination in a disease termed by him "progressive infantile sclerosis." But in Schilder's disease the reports so far available on the histological behaviour of the oligodendroglia, do not allow a general application of this finding. In our own cases we regard the changes of the oligodendroglia as secondary. Swelling of the oligodendroglia is seen only in one case, in a zone where it can be interpreted as a result of the particularly intense process of destruction. The diminution of the oligodendroglia in the centre of the process can also be considered as a secondary phenomenon, the more so as we do not know enough about its possible participation in the formation of granular compound cells.

We have not yet reported the changes found in the peripheral optic system. There was in both of our cases irregular demyelination of the chiasma, extending to the optic nerves. In coronal sections of both our cases the peripheral, and more particularly the ventral, part of the optic tract is better preserved than the central and the upper part (fig. 4, *a* and *b*). This is also seen in the third familial case not yet published (fig. 4, *c*). Occasionally the lesion is confined to the centre (fig. 4, *c*). Fat stain shows the process to be the same as that found in the cerebral white matter. At the zone of demarcation one finds a layer of fat-laden globoid cells, indicating that the lesion is proceeding from the centre towards the periphery (fig. 4, *d*). This is of pathogenic interest because Monnier and Walthard [28] described recently similar centrally placed lesions of the optic tract in a case of cerebral lues, in which the anterior choroid artery supplying a part of the optic tract was found to be obliterated. This might suggest a vascular origin of the changes in the optic tract in cases of Schilder's disease.

There is no systematic limitation of the lesion to functional units, although it is obvious that, according to the scheme of Brouwer and Zeeman [9, 10] and others, the papillo-macular bundle must have suffered first and to the greatest degree. Equally interesting is the striking similarity of the lesions of the optic tract to those found by Scherer [30] in the well-known disease in monkeys: the lack of peripheral optic lesions in Schilder's disease was one of the reasons that Schob [32] and Spielmeyer [36] would not accept a close relationship between both these conditions. Furthermore gastro-intestinal disturbances, so outstanding a feature in Schob's and Scherer's disease in monkeys, are not foreign to Schilder's disease, as exemplified by Globus' [18] and our own cases. The same applies to "honey-combed" lesions in the spinal cord found in the monkeys, which made Scherer think of a condition related to pernicious anæmia. Honeycombed lesions occur in Schilder's disease (Wertham [39], Marinesco and co-workers) [27] and they might be found more frequently if more attention were paid to the point. There is no necessity to interpret the case described by the Roumanian authors as a combination of Schilder's disease and ophthalmo-neuromyelitis.

Histopathological similarities do not necessarily indicate a close ætiological relationship, as pointed out by Spielmeyer [35]. Moreover, since Schilder's disease is not likely to be a disease entity, findings seen in one of its groups need not apply to another. The fact, however, that an apparently epidemic and transmissible (Gaertner) [16, 17] disease and cases of Schilder's disease of heredofamilial nature have so much in common, presents an interesting pathogenic problem requiring further attention.

SUMMARY.

The clinical and pathological records of two brothers suffering from Schilder's disease are presented. Their mother is affected by a progressive spinal condition the nature of which is still uncertain.

Gastro-intestinal troubles preceded by a long interval the nervous affection of the two brothers. These symptoms are also presented by a third brother who has slight ataxia.

There were no histological changes in the visceral organs to account for the affection of the central nervous system.

The pathogenic and ætiological views on Schilder's disease are discussed in the light of the cases investigated. Consideration is given to

the theory of primary glial affection with special regard to the difficulties of interpretation of the histological data.

The peculiar distribution of the process in the optic tract is described. It was similar to that described by Scherer in a spontaneous disease in monkeys. The nosological significance of these symptoms and of "honeycombed" patches, which are found also in Schilder's disease, is discussed as to its broader aspects.

We desire to express our thanks to Mr. C. Geary, who kindly gave us those sections he had prepared of the first case, and to Mrs. Meyer for the histological and microphotographic work in relation to both cases. We should also like to take this opportunity of expressing our thanks to Dr. Golla, Director of the Central Pathological Laboratory, and to Dr. Mapother, Medical Superintendent of the Maudsley Hospital. We wish to express our indebtedness to the Rockefeller Foundation, who gave a grant to one of us (A.M.); also to the Medical Research Council for a grant made for incidental expenses.

REFERENCES.

[1] Bailey, P., and Schaltenbrand, G. *Zeitschr. f. Nervenheilk.*, 1927, **97**, 231.

[2] Bielschowsky, M., and Henneberg, R. *Journ. f. Psychol. u. Neurol.*, 1928, **36**, 131.

[3] Bielschowsky, M., and Maas, O. *Ibid.*, 1932, **44**, 133.

[4] Bodechtel, G., and Guttmann, E. *Zeitschr. f. d. g. Psychiatr. u. Neurol.*, 1931, **133**, 601.

[5] *Idem. Ibid.*, 1932, **138**, 544.

[6] Bogaert, L. v., and Bertrand, J. *Rev. Neurol.*, 1933, **2**, 249.

[7] Bogaert, L. v., and Scholz, W. *Zeitschr. f. d. g. Neurol. u. Psychiatr.*, 1932, **141**, 510.

[8] Bouman, L. "Diffuse Sclerosis." London, 1934.

[9] Brouwer, B., and Zeeman, W. P. C. *Brain*, 1926, **49**, 1.

[10] Brouwer, B., Zeeman, W. P. C., and Houwer, A. W. H. *Schweiz. Arch. f. Neurol u. Psychiatr.*, 1923, **13**, 118.

[11] Cheng Yü Lin. *Arch. of Neurol. and Psychiatr.*, 1934, **31**, 1247.

[12] Collier, J., and Greenfield, J. G. *Brain*, 1924, **47**, 489.

[13] Davison, C. *Arch. of Neurol. and Psychiatr.*, 1933, **30**, 75.

[14] Ferraro, A. *Ibid.*, 1928, **20**, 1065.

[15] *Idem. Psychiatr. Quart.*, 1933, **7**, 267.

[16] Gaertner, W. *Klin. Wochnschr.*, 1932, **2**, 905.

[17] *Idem. Arch. f. Psychiatr. u. Nerv.*, 1933, **99**, 822.

[18] Globus, J. H. In W. Penfield: "Cytology and Cellular Pathology of the Central Nervous System." New York, 1932, **3**, 1145.

[19] Greenfield, J. G. *Proc. Roy. Soc. Med.*, 1933, **26**, 18.

[20] Hallervorden, I., and Spatz, H. *Arch. f. Psychiatr. u. Nerv.*, 1933, **98**, 641.

[21] del Rio Hortega, P. *Memorias de la Real. Soc. Esp. de Hist. Nat.*, 1928, **14**, 5.

[22] Kaltenbach, H. *Zeitschr. f. d. g. Psychiatr. u. Neurol.*, 1922, **75**, 138.

[23] Krabbe, K. *Brain*, 1916, **39**, 74.

[24] Levaditi, C. *Ann. de l'Inst. Pasteur*, 1930, **45**, 673.

[25] Levaditi, C., Lepine, P., and Schoen, R. *Compt. rend. Soc. de Biol.*, 1930, **54**, 986.

[26] Macnamara, E. D., and Dickson, W. C. *Proc. Roy. Soc. Med.*, 1933, **26**, 297.

[27] Marinesco, G., State Draganesco, Sager, O., and Grigoresco, D. *Rev. Neurol.*, 1930, **2**, 193.

[28] Monnier, M., and Walthard, K. M. *Monatschr. f. Psychiatr. u. Neurol.*, 1934, **90**, 60.

[29] Patrassi, G. *Virchow's Archiv*, 1931, **281**, 98.

[30] Scherer, H. J. *Zeitschr. f. d. g. Neurol. u. Psychiatr.*, 1932, **141**, 212.

[31] Schlesinger, B., Greenfield, J. G., and Stern, R. O *Arch. Dis. in Childhood*, 1934, **9**, 49.

[32] Schob, F. *Zeitschr. f. d. g. Neurol. u. Psychiatr.*, 1931, **136**, 95.

[33] Scholz, W. *Monatschr. f. Psychiatr. u. Neurol.*, 1933, **86**, 111.

[34] *Idem. Zeitschr. f. d. g. Neurol. u. Psychiatr.*, 1925, **99**, 651.

[35] Spielmeyer, W. "Verhdl. deutsche Nervenaerzte." Leipzig, 1929, 86.

[36] *Idem. Zeitschr. f. Hyg. u. Infektionskrankh.*, 1931, **113**, 170.

[37] Stewart, T. G., Greenfield, J. G., and Blandy, M. A. *Brain*, 1927, **50**, 1.

[38] Strauss, M. B., Heath, C. W., and Castle, W. B. *Amer. Journ. Med. Sci.*, 1931, **182**, 741.

[39] Wertham, F. *Arch. of Neurol. and Psychiatr.*, 1932, **27**, 1380.

[40] Witte, F. *Münch. med. Wochnschr.*, 1921, **68**, 69.

THE PHYSIOLOGICAL PATHOGENESIS OF EPILEPSY.[1]

BY WILLIAM G. LENNOX, M.D.

WHEN Hippocrates made the bold prediction that whoever learned to make the epileptic humid or dry, hot or cold, could cure his disease, he had a conception, the essential rightness of which the medical world is only now appreciating. We now know that certain alterations of the physiology of the body, though they do not cure epilepsy, may modify the frequency or force of epileptic seizures. Induction of alkalosis by means of hyperpnœa, or by the ingestion of large amounts of alkali, tends to precipitate seizures. Acidosis (induced by starvation, by ingestion of a ketogenic diet or of acids or acid-forming salts, by breathing of air rich in carbon dioxide, or by increasing the concentration of the lactic acid of the blood through muscular work) tends to decrease seizures in certain individuals having very frequent attacks. Again, the retention of fluids by the body, secured by the injection of pitressin with simultaneous ingestion of large amounts of water, may precipitate convulsions, whereas a severe limitation of the fluid intake inhibits them. These matters have received consideration in previous publications and will not be dealt with now. I shall attempt only to review recent studies from our own laboratories which deal with the rôle in epilepsy of the cerebral circulation and of oxygen metabolism.

The question must first be answered, "Is there evidence of a specific defect in the cerebral circulation or in the oxygen metabolism of epileptics?" Spasm of the arterioles of the brain with resulting generalized cerebral anæmia has been a favourite theory in explanation of the sudden onset of seizures. The theory is excellent; the experimental proof a failure. Dr. and Mrs. Gibbs and I [1] have recorded the flow of blood through the brains of patients by means of a thermo-electric flow recorder inserted into an internal jugular vein. Records were secured of ten patients having either spontaneous or induced fits. There was no decrease in the blood flow immediately before a spontaneous seizure. We believe that the theory of a generalized cerebral anæmia as a cause of spontaneous seizures should be placed reverently in the museum of outmoded medical theories. The possibility of a spasm of a single vessel with a resulting localized area of anæmia remains. Two bits of evidence are against: following the constriction of single cortical vessels frequently observed *by* neurosurgeons, muscle spasm or paralysis does not ordinarily ensue; and the induction of generalized cerebral anæmia (with consequent local anæmia) is not a certain method of precipitating a seizure in the ordinary epileptic. However, this question of localized vascular spasm requires more study.

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[1] Read before the International Neurological Congress in London on July 28, 1935. This is No. XX in a series entitled "Studies in Epilepsy," aided by a grant from the Harvard Epilepsy Commission.

A continuous and sufficient supply of oxygen is essential for the proper functioning of nervous tissues. Denial of oxygen to the brain for a few seconds results in unconsciousness and tonic muscle spasm. We determined, therefore, to submit the relationship of oxygen and seizures to careful study.

Is the total volume of oxygen consumed by patients normal? Between seizures the oxygen consumption is normal or only slightly reduced. Of more significance is the fact that immediately before and during non-convulsive seizures there is no alteration in the total oxygen consumption of the body. I have numerous records of *petit mal* seizures which have occurred while patients were attached to a metabolism machine for measuring oxygen consumption. Portions of the breathing records of four patients are shown in fig. 1. In none does the occurrence of a seizure significantly influence the smooth upward slope of the curve which indicates the volume of oxygen consumed.

Is the oxygen tension of the circulating blood normal? Mrs. Gibbs and I have measured the oxygen content of the blood of a large group of patients, taking blood from an artery, and also from an internal jugular and from a basilic or femoral vein. The arterial blood is of first importance in examination, for a gross defect in the tension of oxygen going to the brain would be of obvious significance. We measured the oxygen saturation of the arterial blood of eighty-eight patients. In only 54 per cent. was the saturation within the range commonly accepted as normal; namely, between 94 and 99 per cent. The deficiency was, however, small. Only 11 per cent. of the bloods were less than 90 per cent. saturated. Furthermore, this defect was not confined to epileptics. Fifty-eight non-epileptic patients of the neurological ward were examined and an even smaller proportion, 46 per cent., had a normal oxygen saturation. We found that if patients with a deficient saturation were made to breathe oxygen or even to respire deeply, the saturation became normal. The difficulty, therefore, is due to an insufficient pulmonary ventilation, the consequence of poor posture, and poor physique [2].

The venous blood from the arm was examined in one hundred instances. The average oxygen saturation (65 per cent.) is definitely lower than the normal (72 per cent.) which is the average figure culled from the literature. These findings point to a slow flow of blood through the extremities of these patients.

Is there also an abnormally low oxygen tension of the blood leaving the brain? In an effort to secure conclusive evidence on this vital point, we measured the oxygen content of blood from the internal jugular vein in 130 instances. The average oxygen saturation of 63 per cent. was even less than the saturation of blood from the arm. However, we found that patients without epilepsy or cerebral disease had an equally low saturation. Furthermore, blood drawn from an internal jugular vein during a mild seizure or during status epilepticus was found to have an oxygen saturation within normal limits [3].

The hypoxæmia of arterial and of arm vein blood encountered in a large proportion of epileptics is an expression of the stagnant physical and mental state which so often accompanies epilepsy. The hypoxæmia when present requires correction, but it cannot be a fundamental factor in the causation of seizures.

We have failed to find evidence of a defect in the supply of blood or of oxygen to the brain of epileptics. The next question is whether the frequency of seizures will be changed if the blood or oxygen supply is artificially altered. Eight years ago [4, 5], I reported that *petit mal* seizures could be induced in patients having very frequent *petit mal* if they breathed air poor in oxygen, but not so poor as to produce unconsciousness in the normal person. I have now encountered thirteen of these patients whose *petit mal* attacks could always be induced by means of an artificially induced anoxæmia. I emphasize that these were patients having from ten to several hundred *petit mal* daily. In patients with only occasional *petit* or *grand mal*, attacks are not easily induced. We produced complete unconsciousness by having patients breathe nitrogen or by causing them to faint. Syncope was induced by giving the patient sodium nitrite and then, with the aid of a tipping table, standing him erect. Of twenty *grand mal* patients rendered unconscious by cerebral anæmia or anoxæmia, only one experienced his usual convulsion. Presumably *petit mal* is more readily induced than *grand mal* because of greater frequency and lower threshold, and not because of a different intrinsic mechanism, though further study may alter this view.

In order to test the effect of the opposite condition, an over-abundance of oxygen, Dr. Behnke and I placed three patients having very frequent *petit mal* in a pressure chamber under from one to four atmospheres of absolute pressure. In the chamber the number of spontaneous seizures was 55 per cent. of the patient's usual number. Previous observations with these patients had shown that seizures in each could be regularly induced by a certain period of over-ventilation.

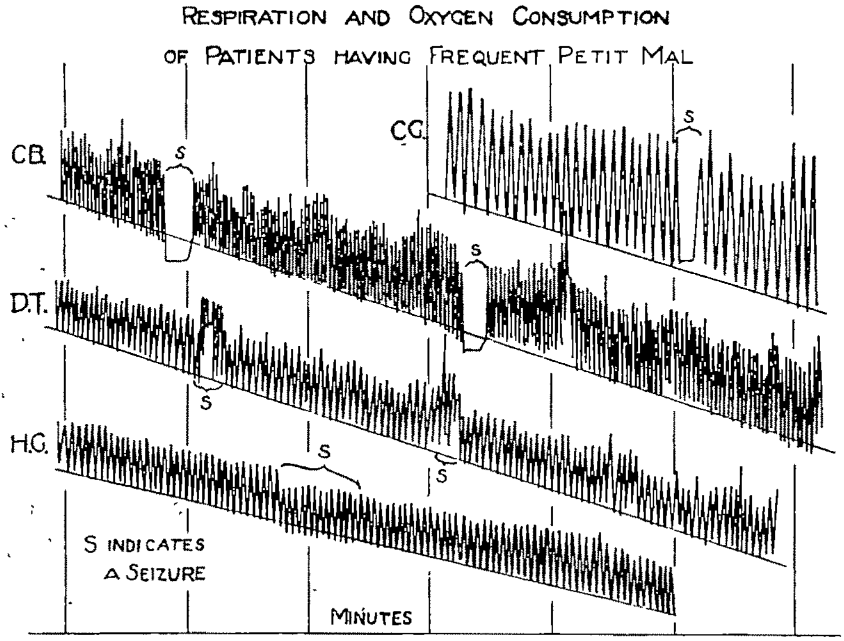

FIG. 1.—Graphic record of the oxygen consumption of four patients, as indicated by their initials. The patient was attached to a machine for measuring the basal metabolism. The records read from right to left. The upward slope of the base line indicates the volume of oxygen consumed. The excursions of the pen record the frequency and depth of respirations. The period occupied by a seizure is indicated by the letter S. There is no significant alteration in the oxygen consumption either before or during seizures.

While patients were in the chamber under pressure they performed hyperpnœa in an atmosphere of oxygen, and by this means a tension of oxygen twenty times the usual atmospheric tension was obtainable. It was found that with progressive increase in the tension of oxygen, there was progressive increase in the amount of over-ventilation required to produce a seizure. With an oxygen tension twenty times normal, five times the usual amount of over-ventilation was required [6].

These observations demonstrate that acute decrease in blood or oxygen supply to the brain may precipitate, and acute increase in the oxygen supply may inhibit a patient's seizures.

The epileptic seizure has been compared to a reservoir impounded by a dam [7]. The springs which give rise to the imprisoned water (viz. heredity, abnormalities of the brain or of the body, disturbances of the sympathetic nervous system and of the emotions) are the fundamental causes of the attacks. A seizure, represented by an overflow of the dam, can result either from an increase in the height of the waters, or from a decrease in the height of the dam. I believe the physiological changes which we have been discussing are not the waters within, but the bank without; they act by altering seizure threshold. Obviously, raising the banks may be of only slight or temporary advantage to the patient.

These various approaches to the ætiology of epilepsy lead to a question which has been a closed door before which clinicians and investigators have come to a stand. What takes place in the brain when a seizure occurs? Thanks principally to Berger, we no longer have to depend on the circumstantial evidence of sensation or of muscle contraction. As through a door unexpectedly opened, we can perceive what is taking place within the brain. We can discard figures of speech and speak plainly of the electrical activity of the brain, and can make graphic record of this activity.

Dr. Frederic Gibbs, Dr. Hallowell Davis and I, working in the Department of Physiology of Harvard Medical School, have obtained records of the electrical potentials from the brains of twenty-one patients during hundreds of seizures. The methods and apparatus used and the observations made are presented elsewhere in detail which is impossible here [8].

In the case of *grand mal*, for a variable period before the convulsion there is an increase in the electrical activity of the brain; during the convulsion waves are slower and of very large potential; and in the period of stupor following the convulsion, there is almost complete absence of electrical activity.

Because impairment of consciousness is the essential feature of a seizure and because the muscular movements of a convulsion add complications to the record, I shall speak from now on only of *petit mal*. *Petit mal* are invariably accompanied by a burst of action potentials much larger and less frequent than the patient's usual potentials. From a frequency of 10 to 20 a second they slow to 1 to 3 a second, and from a voltage of 10 to 50 millivolts they increase to 100 to 300 millivolts.

These waves definitely represent potentials set up by discharging cells in the brain, and not the potentials of contracting muscles in the scalp or in cerebral arteries. During *petit mal* any slight twitching movements of the face are synchronous with the large waves. But similar movements made voluntarily by the patient when conscious are not attended by changes in the waves.

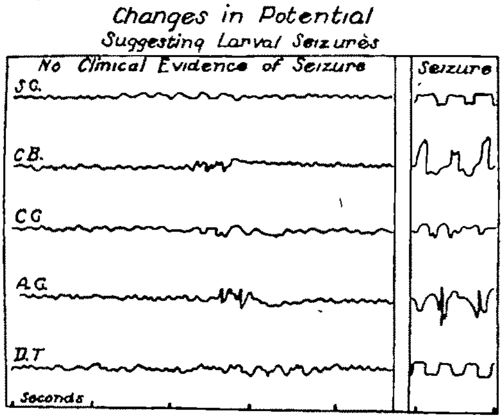

FIG. 2.—Electro-encephalograms of five patients when having *petit mal* (right hand portion) and when free of symptoms (left hand portion). The small alterations in potential during symptom-free periods resemble miniature *petit mal* waves.

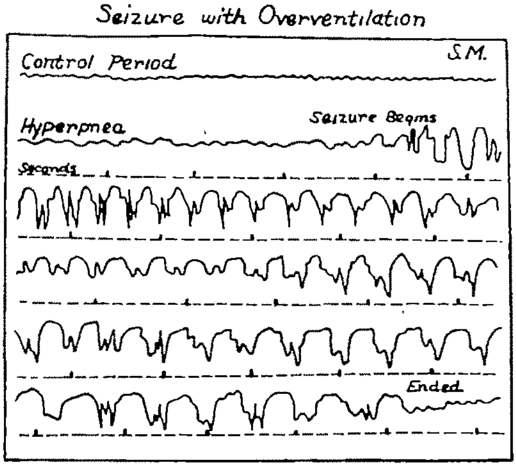

FIG. 3.—Electro-encephalogram of patient S.M. before and during hyperpnœa, and the resulting *petit mal* seizure. The upper tracing is during a conscious period. The remaining tracings are a continuous record. In the record labelled "hyperpnœa" (after the patient had been performing voluntary over-ventilation for about two minutes) the action potentials are large, slow and irregular. The seizure begins at the end of this line and continues for twenty seconds. The patient, of course, stopped over-ventilation with the onset of the seizure.

The final proof that we were dealing with brain activity was obtained by placing the needle electrode directly into brain substance. Simultaneous tracings taken from the motor area of the brain and from the scalp exhibit differences in the shape of the waves, but a momentary lapse of consciousness, when it occurs, is unmistakable in both tracings.

We have records of spontaneous *petit mal* from thirty-two patients. These records are alike in the large slow waves which replace the ten a second rhythm, but the details of the waves are individual for each patient. The waves during a portion of a *petit mal* are shown for five of the patients in the right hand panel of fig. 2. A complete *petit mal* (induced, but of the same form as this patient's spontaneous seizure) appears in fig. 3.

Of great interest is the appearance in the records of these patients (at times when they are free of any objective or subjective evidence of seizure) of small alterations in potential which are indistinguishable from the onset of that patient's seizure (fig. 2). Non-epileptic patients, when awake, never show these disturbances. We regard them as larval or subthreshold seizures. Electro-encephalograms may possibly provide a means of detecting the epileptic state of an individual, even in the absence of seizures.

We now turn to the question of the effect of changes in the physiology of the body on the electrical activity of the brain with respect to seizures. In both normal and epileptic persons the induction of alkalosis by hyperpnœa, of anoxæmia by breathing of nitrogen, or of cerebral anæmia by induced syncope, causes the action potentials of the brain to become slower and larger. When an attack is induced in an epileptic patient by one of these methods, these large waves merge into the waves of the induced seizure. The waves of the induced and of the spontaneous attack are identical. The seizure waves are clearly distinguishable by their regularity and their individual form, and especially by the sharp spike of negative potential. Fig. 3 demonstrates the alteration of electrical activity associated with a short period of hyperpnœa which was followed by seizure, and fig. 4 shows the alteration during unconsciousness from syncope together with the waves of the *petit mal* seizure which was thereby induced.

The fundamental clinical feature of an epileptic seizure is the impairment of consciousness. The states which we have been considering, acute alkalosis, anoxæmia and anæmia, also involve disturbances of consciousness. Also, in sleep, both normal and narcoleptic, and even in mental inattention, electrical potentials become larger and slower. Clinically, all these are states which favour the occurrence of seizures. In the electro-encephalogram, it looks as though the type of electrical activity which accompanies these states integrates with and discharges the patient's neurological seizure mechanism.

What is the meaning, in terms of cerebral activity, of these large slow waves? One possible view is this. In normal activity, there are many clusters of neuronal cells discharging, not in unison, but in harmony. The usual rhythm of 10 to 20 discharges a second is a mosaic of the activity of many centres. In a *petit mal*, many waves become one. The large waves represent not a suppression or an augmentation, but rather a synchronization of various discharging cell clusters. There is integration of activity as regards timing, but disintegration as regards the delicate and complicated interplay of various discharging nuclei. The harmony of the symphony orchestra has become a single note. The representative constitutional government has become a totalitarian state.

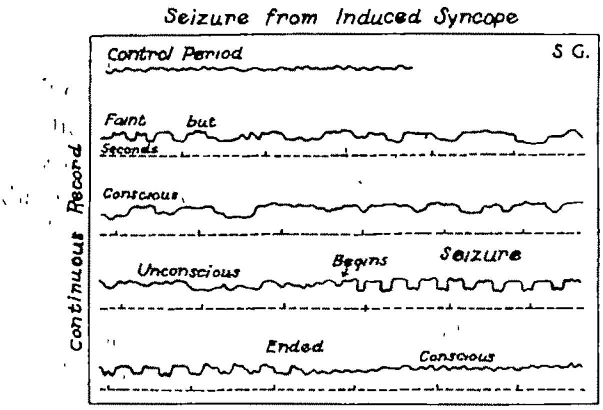

FIG. 4.—Electro-encephalogram of patient S. G., before and during syncope and the *petit mal* seizure. He was given four grains of sodium nitrite by mouth and after fifteen minutes was stood upright. The last four tracings are a continuous record. During the first tracing he was pale and faint but conscious. Within several seconds after losing consciousness, a *petit mal* attack, recognized by twitching movements of the eyebrows, began and lasted five seconds. As soon as he was unconscious, he was placed in a horizontal position and with the cessation of the seizure was again conscious.

What is the origin of this sudden synchronization in which the individuality of discharging nuclei is lost? It cannot be primarily any organic disease of the brain because structural defects are constant, whereas seizures are periodic. There must rather be transient alterations either in the pathways taken by nerve impulses, or in the electrical activity of certain clusters of cells. There is growing evidence of an essentially neural mechanism capable of producing unconsciousness and muscle spasm without the intervention of physiological changes which involve the whole brain. I am thinking especially of cases of reflex epilepsy, of unconsciousness from an irritable carotid sinus, without circulatory changes, and of experimental evidence provided by F. A. and E. L. Gibbs [9], that certain areas of the brain have a very low threshold for convulsions electrically induced. We hope further study will disclose the point of origin and the pathway of spread of the electrical potentials associated with seizures. In conclusion, our hope of learning the pathogenesis of epilepsy, so far as it concerns physiology and so far as it has therapeutic approach, rests on finding the physico-chemical process involved in the electrical activity of the neurone. We can hardly expect to arrive at the solution of this problem, which is so closely linked in epilepsy with the mysterious problem of heredity. Yet we have our rewards. "To journey hopefully," said Stevenson, "is a better thing than to arrive." We therefore travel with hope on this long and winding road, the end of which is the end of epilepsy.

REFERENCES.

[1] Gibbs, F. A., Lennox, W. G., and Gibbs, E. L. "Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man," *Arch. Neurol. and Psychiat.*, 1934, **32**, 257.

[2] Lennox, W. G., and Gibbs, E. L. "The Oxygen Saturation of the Arterial Blood in Epilepsy," *Ibid.* (In press.)

[3] *Idem.* "The Blood Draining the Brain and the Limbs of Epileptics with Reference to its Oxygen Saturation," *Ibid.* (In press).

[4] Lennox, W. G. "The Effect on Epileptic Seizures of Varying the Composition of the Respired Air," *Journ. Clin. Investigation*, 1928, **6**, 23.

[5] Lennox, W. G., and Cobb, S. "Epilepsy from the Standpoint of Physiology and Treatment," Baltimore, 1928.

[6] Lennox, W. G., and Behnke, A. R., Jr. "The Effect of Increased Oxygen Pressure on the Seizures of Epilepsy," *Arch., Neurol. and Psychiat.* (In press.)

[7] Lennox, W. G. "The Multiple Causes of Seizures in the Individual Epileptic Patient," *New England Journ. Med.*, 1933, **209**, 386.

[8] Gibbs, F. A., Davis, H., and Lennox, W. G. "The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness," *Arch. Neurol. and Psychiat.*, 1935, **34**, 1133.

[9] Gibbs, F. A., and Gibbs, E. L. "The Convulsive Threshold of Various Parts of the Cat's Brain," *Arch. Neurol. and Psychiat.*, 1935, **35**, 109.

THE ANATOMICAL LOCALIZATION OF THE HYPOTHALAMIC CENTRE FOR THE REGULATION OF TEMPERATURE.[1]

BY C. H. FRAZIER, BERNARD J. ALPERS AND F. H. LEWY (PHILADELPHIA).

INTRODUCTION.

IT has been abundantly shown that the hypothalamus is important for the normal regulation of body temperature. The evidence for this has been reviewed so frequently in recent years that it hardly bears repetition (Bazett, Alpers, Erb [1]). While Isenschmid and Krehl [2] and Isenschmid and Schnitzler [3] indicated that it was necessary to maintain intact the hypothalamus in order to maintain normal body temperature, they failed to specify definitely the exact region of the hypothalamus necessary for this control. Furthermore, as will be seen subsequently, the area which they indicate differs with our findings. Some attempt was made to locate more specifically the temperature regulating area in the hypothalamus by Bazett, Alpers and Erb, who found in cats that the area in the walls and floor of the third ventricle was most essential for this function. This was carried still further by the studies of Alpers [4], who studied two cases of tumour in the pituitary area in which death was accompanied by severe hyperthermia and loss of temperature control. In these cases it was found that the lesions were in the floor of the third ventricle, more particularly in the substantia grisea. The more lateral and dorsal portions of the hypothalamus were intact.

On the basis of these observations, further experimental studies were undertaken in cats in order to determine whether lesions placed in the substantia grisea in the floor of the third ventricle would produce loss of temperature control. It is these experiments which we now record.

TECHNIQUE.

Cats were used exclusively. They were anæsthetized with sodium amytal injected into the abdominal cavity. The cat was then fitted into a Horsley-Clarke frame and measurements made for destruction of the substantia grisea of the third ventricle. Under aseptic precautions two trephine holes were made in the skull, and through these an electrode was introduced and minute lesions made bilaterally in the floor of the third ventricle. The spherical model of the Horsley-Clarke machine was used. This permitted an approach to the desired part from all angles. The animals were then placed in a specially prepared room with constant temperature and humidity. Temperature readings were made daily. The response of the cats to elevation and depression of temperature was studied. The former was observed by placing some of the animals in an autoclave for five to ten minutes and studying their temperature and the respiratory responses. The latter was studied by exposing the animal to a temperature of 2-6° C., observing the temperature, shivering, and vasomotor responses. The autoclave experiment was abandoned in our later animals, and the response to elevation of temperature studied by raising the temperature of the control room. In all instances the animals were sacrificed by chloroform anæsthesia and the brains removed without delay. Serial section studies were made of the brain-stem, alternate sections being stained with hæmatoxylin-eosin and Weil's myelin sheath stain.

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[1] From the Laboratories of Neurosurgery and Surgical Research in the University of Pennsylvania. Read before the Second International Neurological Congress, London, August 29 to September 3, 1935. This research was aided by a grant from the Rockefeller Foundation.

EXPERIMENTAL RESULTS.

Thirty cats were operated on. In only a small number of these were the lesions placed exactly in the desired situation. In most of the animals the lesion was either too far lateral in the hypothalamus or it was unilateral. In those instances in which the lesions were properly placed, the loss of temperature regulation was complete. Cat 13/10 affords an excellent example of this. In this animal the lesions were

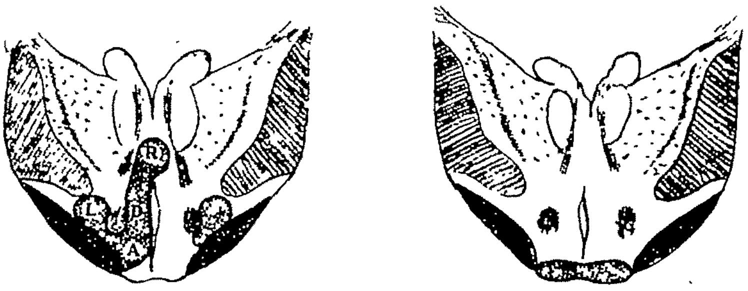

FIG. 1.—On the left diagram the dotted areas show the regions which can be destroyed without loss of temperature control. On the right the dotted area, occupying the main position of the N. anterior hypothalami, is indispensable for normal regulation of temperature.

placed in the floor of the third ventricle. This animal had total loss of temperature control: it was completely thermolabile. At room temperature its rectal temperature was 24° C. (Table I). In a warm room with a temperature of 32° C. its temperature rose to 38° C., and fell to 34° C. after twenty minutes exposure in a cold room at 2·5° C. The temperature continued to fall in the cold room, so that after five hours it was 15° C. There was no hyperpnœa, no true panting and no evidence whatever of shivering. Vasomotor responses in the foot-pads were totally lacking. Necropsy revealed bilateral lesions in the floor of the third ventricle. These proved on serial section of the hypothalamus to involve the substantia grisea of the third ventricle. The other hypothalamic nuclei, the N. paraventricularis, the N. supraopticus, the N. lateralis hypothalami, and the N. mammillaris were all intact. There were discrete lesions only in the substantia grisea.

TABLE I.

Post-operative day	Environmental temp.	Cat temp.	Pulse	Resp.	Remarks
1	27° C.	24° C.	Irregular	6	Stuporous.
2	32° C.	38° C.	140	21	Cat active. Bites and scratches. No hyperpnœa.
	2·5° C.	36° C. (after 12 min.)	124	19	
		34·5° C. (after 20 min.)	92	18	No shivering response.
	Room temp	38·5° C.			
4	2° C.	30° C. (after 2 hrs.)	96	30	
		15° C. (after 6¼ hours)	Not perceptible	Not perceptible	No shivering response.

Responses of cat 13/10 to heat and cold. There is complete thermolability with no hyperpnœic or shivering response.

Cat 13/10 represents a typical example of complete temperature loss, and is characteristic of animals in which the temperature-regulating area has been effectively destroyed. In this animal serial section studies of the hypothalamic area revealed a complete destruction of the N. hypothalamicus anterior (Rioch) or the substantia grisea which lies in the floor of the third ventricle. The destroyed area extended from the anterior part of the optic chiasm to the infundibular region.

In animals in which the lesion was not placed so as to cause a complete loss of temperature control, there were manifestations of partial loss. Cat 10 was a case in point. This animal survived five days after operation. It had a markedly subnormal temperature for twenty-four hours after operation. There was a moderate thermolability which was seen more definitely in a hot than in a cold environment. In the hot-moist control room the temperature and respiration rose definitely. It dropped moderately in the cold room. There was never a complete loss of control because both hyperpnœic and shivering responses could be elicited at some times, but not at others. There was, therefore, in this cat a disturbance in heat control on both the heat-loss and heat-

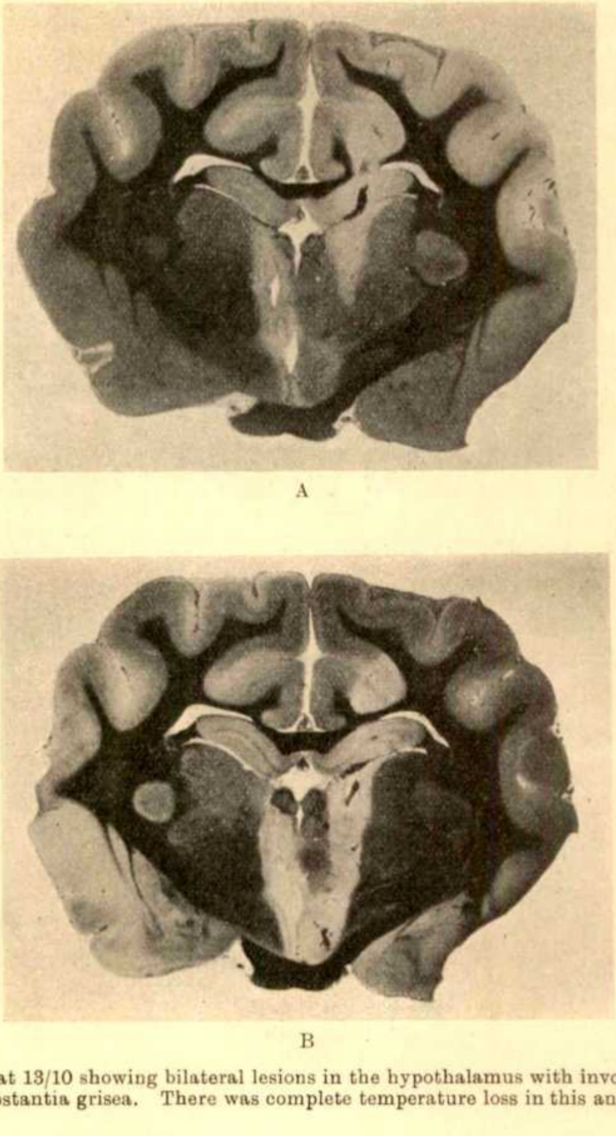
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FIG. 2.—Cat 13/10 showing bilateral lesions in the hypothalamus with involvement of the substantia grisea. There was complete temperature loss in this animal.

producing sides, but only of a relative nature. In contrast to Cat 13/10, the necropsy in Cat 10 revealed a unilateral lesion in the anterior part of the hypothalamus destroying the median portion of the thalamus, the N. reuniens and the N. anterior hypothalamici. The lesion extended laterally in its lower portions and did not involve the grey matter in the floor of the third ventricle. This is an instance, therefore, of a minor disturbance in temperature produced by a unilateral lesion which involved the lateral portions of the hypothalamus, and spared in part the vital area which is important for temperature control, the substantia grisea.

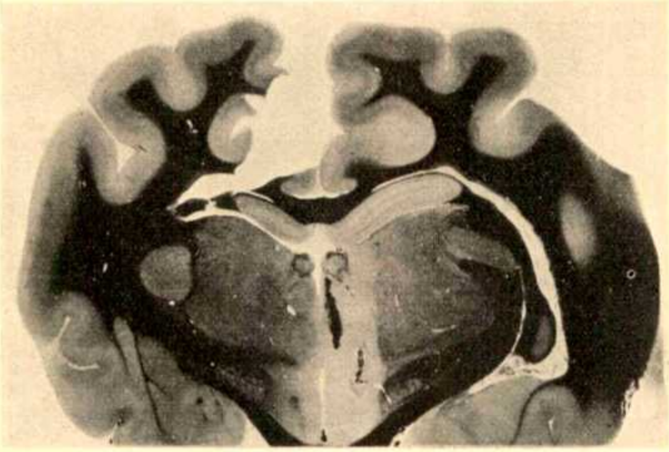

FIG. 3.—The unilateral lesion of the hypothalamus (Cat 10) with only minor disturbances in temperature control.

TABLE II.

Post-operative day	Environmental temp.	Cat temp.	Pulse	Resp.	Remarks
1	25·0° C.	25·5° C.	88	12	
	5° C.	25·5° C. (after 6 min.)		16	Definite shivering after 6 minutes.
		25·5° C. (after 12 min.)			
		26·0° C. (after 15 min.)	84	20	
2	28° C. (moist room)	40·2° C.	200	100	No hyperpnœa or polypnœa.
	27° C. (dry room)	39·5° C.			
	6° C.	38° C.	168	66	No shivering responses.
4	30° C.	40·5° C.	168	64	
	5° C.	38° C.	160	60	

Temperature responses in a cat (Cat 10) in which there was a unilateral lesion destroying only part of the substantia grisea and extending laterally into the hypothalamus.

That there may be relative hypothermia with disturbance of shivering and panting responses in unilateral laterally-placed lesions is illustrated by Cat 87, in which the lesion was in the lateral portion of the hypothalamus, not far from the vital area. This animal showed some tendency to hypothermia, with no shivering or panting responses.

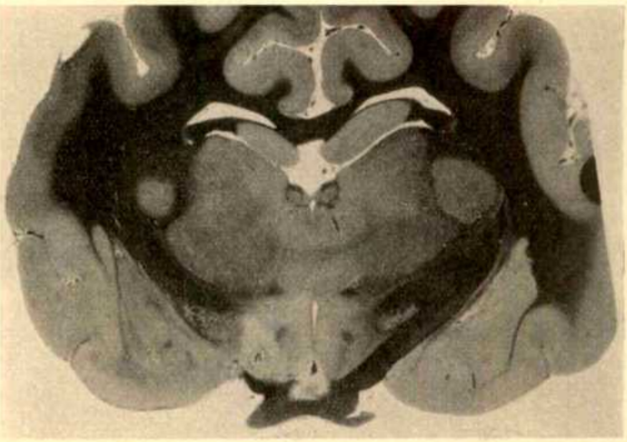

FIG. 4.—Involvement of the nucleus lateralis with only minor disturbances in temperature control.

TABLE III.

Post-operative day	Environmental temp.	Cat. temp.	Pulse	Resp.	Remarks
1	Room temp.	41° C.	200	40	
2	,, ,,	34½° C.	142	24	
	5° C.	34° C.		28	No shivering.
	80° C.	32·5° C.		28	No panting.
		36° C. (after 6 min.)	156	32	No vasometer response.
4	28·5° C.	35° C.	144	24	
	5·5° C.	36° C.	180	24	No shivering.
	80° C.	35·5° C.	188	24	No panting.

A unilateral lesion (Cat 87) involving the N. hypothalamicus lateralis, with persistent hypothermia and no shivering or panting. Disturbance of temperature regulation was only relative and not complete.

Necropsy revealed a large area of necrosis involving the N. hypothalamicus lateralis (Rioch) or what corresponds in man to the N. tubero-mammilaris. The mesial portion of the hypothalamus was not affected.

It is possible, however, that the disturbance of temperature regulation recorded in Cat 87 may have been transitory, as it lived only four days. Another animal (Cat 84) which had bilateral lesions in the N. hypothalamicus lateralis lived for nine days and revealed very little disturbance in temperature regulation. In any event, one thing seems certain from these experiments, and that is the fact that the lateral portion of the hypothalamic area is not essential for temperature regulation.

TABLE IV.

Post-operative day	Environmental temp.	Cat temp.	Pulse	Resp.	Remarks
1		39·5° C.		36	
3		38·5° C.	96	28	
	+6° C.	37° C.		24	Shivering.
	+80° C.	41° C.			Marked panting.
9		38·5° C.		28	
	5° C.	38° C.		28	Marked shivering.

A cat (Cat 84) with bilateral lesions in the lateral parts of the hypothalamus, with transitory temperature disturbances of a minor degree, which later became adjusted.

COMMENT.

Our experiments demonstrate clearly that the vital area in the hypothalamus for the regulation of temperature in cats is the N. hypothalamicus anterior, which corresponds in man to the substantia grisea in the floor of the third ventricle. Bilaterally placed lesions which destroy this tissue produce severe sustained hypothermia with a loss of function of both the heat-loss and heat-maintenance mechanisms. In no instance were we able to produce hyperthermia by lesions placed in the hypothalamus. Unilateral lesions placed in the vital area are followed by severe transitory disturbance in temperature control, but the results are not permanent.

For the complete loss of temperature control it is necessary to have bilateral destruction of the area concerned: the N. hypothalamicus anterior in cats, and the substantia grisea in man.

Laterally placed lesions in the hypothalamus, even if bilateral, are followed by only a transitory loss of temperature control, which in one of our animals was completely restored by the ninth day after operation.

Attention has been called in previous publications (Bazett, Alpers and Erb; Alpers) to the importance of the mesially located tissue in the floor of the third ventricle. While Isenschmid and Krehl indicated in general the importance of this area, their researches did not disclose the exact region necessary for temperature control in the hypothalamus. They asserted that in the rabbit the most important area is the tuber cinereum, stating also that the region close to the third ventricle is of no greater importance for the regulation of temperature than those more distant. Our findings are in disagreement with this. There appears to be no question that the mesial portions of the hypothalamus in the floor of the third ventrical are most vital for temperature control. The lateral portions are not in themselves essential.

Conclusions.

(1) Mesially placed bilateral lesions in the floor of the third ventricle by means of the Horsley-Clarke apparatus produce complete loss of temperature control.

(2) Laterally placed lesions, whether bilateral or unilateral, cause only transitory and fleeting disturbances of temperature regulation.

(3) The vital area for temperature regulation in the hypothalamus is in the floor of the third ventricle, corresponding to the N. hypothalamicus anterior in cats and the substantia grisea in man.

BIBLIOGRAPHY.

[1] Bazett, H. C., Alpers, B. J., and Erb, W. H. "Hypothalamus and Temperature Control," *Arch. Neur. and Psych.*, 1933, **30**, 728.

[2] Isenschmid, V. R. and Krehl, L. "Uber den Einfluss der Gehirns auf die Warmeregulation," *Arch. f. Exper. Path. u. Pharmacol.*, 1912, **70**, 109.

[3] Isenschmid, V. R., and Schnitzler, W. "Beitrag zur Lokalisation der Warmeregulation vorstehenden Zentralapparates in Zwischenhirn," *Ibid*, 1914, **76**, 202.

[4] Alpers, Bernard J. "Hyperthermia due to Lesions in the Hypothalamus," to be published in *Arch. Neur. and Psych.* Read at American Neurological Assoc., Montreal, May, 1935.

NOTICES OF RECENT PUBLICATIONS.

Handbuch der Neurologie. Herausgegeben von O. BUMKE und O. FOERSTER. Berlin: Springer, 1936.

Five more volumes of this system have appeared. They are so comprehensive that in a review it is possible to indicate only their contents.

Band XVII: *Erkrankungen des Rückenmarks und Gehirns.* S. 575, mit 24 Abbildungen. Price RM. 93.

This volume opens with a long article in English by Kinnier Wilson on "The Epilepsies," in which convulsions are treated as merely symptoms of morbid states whether we can identify these or not. The subject is presented with the clarity and completeness which would be expected of the author. In his chapter on narcolepsy Wilder discusses this interesting subject very fully from the clinical as well as the physiological point of view. Under the title spasmophilia Husler deals with tetany and with other less-defined forms of spasm and convulsions. The clinical features of migraine, their pathogenesis, and their treatment are admirably dealt with by H. Richter of Budapest. He favours the view that the attacks result from angiospastic crises, possibly due to various factors, of the cerebral vessels of the vertebral system. The chapter on the vasomotor and trophic affections, including Raynaud's disease, erythromelalgia, acrocyanoses, acroparæsthesiæ, scleroderma and allied conditions, was originally written by Cassirer but has been revised by R. Hirschfeld. Each of these subjects is excellently presented and the latest investigations on them are incorporated.

Braun analyses and describes some of the commoner psychoneurotic disorders under the heading "Die neurasthenische Reaktion," allotting due importance to both their mental and physical aspects. In the last chapter Jahrreiss of Cologne deals with the so-called organic neuroses, which he defines as the "psychogenesis of bodily disturbances." He discusses in the first place the disorders of the vegetative system which are attributable to mental factors, and finally the occupational neuroses and stammering.

XII u. XIII Bänder: *Infektionen und Intoxikationen.* Bd. XII. S. 776, mit 133 Abbildungen. Price 132 RM; Bd. XIII. S. 1116, mit 212 Abbildungen. Price RM. 192.

These two volumes deal very comprehensively with nervous diseases of infective and toxic origin. The greater part of the first is devoted to syphilitic disorders. Sarbó contributes an excellent article on meningo-vascular affections in acquired and congenital syphilis, but he has devoted so much space to their pathology and to the citation of authorities that the definition of clinical types has suffered. Richter writes on the pathology of tabes dorsalis, maintaining still that the essential cause is development of granulation tissue in the subarachnoid space around the dorsal roots, but he gives adequate attention to other views. Mann deals with the clinical aspects of tabes and its treatment, and Jahnel with general paralysis and trypanosomiasis. Sittig describes in great detail the tubercular diseases of the nervous system, including, in addition to generalized meningitis, circumscribed tubercular meningitis, pachymeningitis tuberculosa, and serous meningitis associated with tuberculosis. Kroll, of Moscow, writes on leprosy and on the nervous complications of typhus fever, and Gamper on chorea. The volume opens with a short chapter on the nervous complications of the exanthemata and of other infectious illnesses.

The first half of Volume XIII is devoted to diseases due to filtrable viruses in which myelitis and disseminated sclerosis are included. Wohlwill deals with herpes zoster, Kroll with rabies, and Pette with the symptoms and anatomical changes in poliomyelitis and postvaccinal encephalitis. The latter section contains a valuable discussion to the nature of acute disseminated encephalomyelitis. Stern, a recognized authority on the subject, writes on epidemic encephalitis, including the allied diseases which have occurred in Japan, Australia, and elsewhere. Köryey discusses myelitis, excluding that due to syphilitic and other recognized pathological agents; consequently, he concentrates mainly on the acute disseminated type. Marburg deals in a masterly manner with the clinical and pathological features of disseminated sclerosis, which he regards as an infectious disease due probably to a virus. The second part of this volume consists mainly of exhaustive articles by Bumke and Krapf on the action of exogenous poisons on the nervous system, and by Bumke and Kant on acute intoxications and drug addictions. Other chapters deal with nervous affections due to metabolic disturbances, diseases of the blood and nutritional disorders; they include a concise but adequate article by Bremer on subacute combined degeneration of the cord, or, as he calls it, funicular myelitis.

Band IX: *Muskeln und Periphere Nerven.* 1935. S. 259, mit 57 Abbildungen. Price RM. 45.

This volume opens with a short but useful chapter on myalgia and myositis by Moser. Wexberg writes on the symptoms and pathology of traumatic lesions of the peripheral nerves and plexuses and on the principles of their treatment, and in a later chapter on neuritis and polyneuritis; in the latter section he includes facial palsy, sciatica, and special affections of other peripheral nerves. The chapter on the neuralgias, also written by Wexberg, is concise but comprehensive; treatment is excellently described. The histology of neuritis is dealt with by Villaverde of Madrid, and tumours of the peripheral nerves by Gagel; both these sections are well illustrated and incorporate the latest views on the pathology of the somatic and sympathic systems.

Band VIII: *Allgemeine Therapie.* S. 749, mit 182 Abbildungen, Price RM. 126.

This volume opens with a concise but valuable chapter by Fröhlich on the pharmacology of drugs which influence the nervous system. In the next Wagner-Jauregg writes on treatment of general paralysis and disseminated sclerosis by induced fever. Lehmann deals exhaustively with the surgical treatment of injuries and diseases of the central and peripheral nervous systems, including the sympathetic, and Hohmann with the orthopædic treatment of palsies. Foerster devotes 100 pages to "Uebungstherapie," that is, the correction or compensation of various motor disturbances by exercise and re-education; he analyses the factors on which success depends and describes fully the methods applicable to different conditions. It is an extremely valuable and unique presentation of the subject. Mann deals at considerable length with electrotherapy, Marburg and Sgalitzer with radiotherapy, Strasser and Wexberg with the influence of baths and climate, and Reinhold with psychotherapy.

All the sections of this important volume, which can be strongly recommended to all neurologists, attain a high standard.

On the Peroneal Type of Progressive Muscular Atrophy. By JULIA BELL. The Treasury of Human Inheritance, Cambridge University Press, 1935. Vol. IV., "Nervous Diseases and Muscular Dystrophies," Part II. Pp. 70, with plates and pedigrees. Price 12s. 6d.

This study contains an account on the usual lines of the clinical course and features of peroneal muscular atrophy. The author notes that the paresis and limitation of movements are in proportion to the muscular wasting, but most observers would maintain that a characteristic of this disease is the mobility which sufferers from it retain for years after profound muscular atrophy below the knees has been present, and much deformity of the feet has developed.

There is a list of other abnormal physical signs in the nervous and other systems that may be found in cases of peroneal muscular atrophy, but no information is given to show whether or not these are simply coincidental phenomena, and no conclusions can be drawn from their presence.

Peroneal atrophy may, it appears, exhibit every type of inheritance, and the author classifies her pedigrees under three headings: Group A, representing sex-linked inheritance, Group B, in which both parents are normal, and Group C, of dominant inheritance in which one or other parent has been affected and the sufferers themselves—whether male or female—are liable to have affected offspring. The large majority of cases of peroneal atrophy fall into Group C.

The study is very diffusely written and expensively produced, and its high cost will seriously limit its circulation amongst those from whom its readers might expect to be drawn. The investigations of which the present study is one, are of great interest to neurologists, and their publication in a more succinct and less expensive form would be widely welcomed.

Études Neurologiques. Par G. GUILLAIN. 6 ième série. Paris: Masson et Cie. 1935. Pp. 430. Price 80 francs.

Those who have enjoyed the previous volumes of this series, with their clinico-anatomical approach to the problems of neurology, will welcome this addition thereto. It covers a wide range of nervous diseases, and includes a long chapter on intracranial tumour as well as shorter studies of cerebral, spinal, peripheral nerve and muscular diseases.

Perhaps the most interesting chapter deals with occupational paralyses of the external popliteal division of the sciatic, and illustrates the anatomical relationships in the region of the knee which is responsible for the paralysis.

The Image and Appearance of the Human Body, By P. SCHILDER, Psyche Monograph No. 4. London: Kegan Paul. 1935. Pp. 353. Price 10s. 6d.

Dr. Schilder's ability in fusing theories and observations here results in a fluent and coherent account of the part the body-schema can be conceived to play in a physiological psychology. Head and Freud are the two chief sources of his theory, though Goldstein, Kohler and many others have also been laid under contribution. It is not the views he presents, but the boldness and dexterity with which the author moulds them together that gives the work its original and interesting flavour.

Psycho-analytic interpretations of human conduct and thought are so essential to his thesis that the non-Freudian reader will find the book a stimulating essay rather than a report of an empirical investigation, which it is intended to be.

Chagrins d'amour et psychoses. Par CONSTANCE PASCAL. Paris: G. Doin. 1935. Pp. 168. Price 16 francs.

The authoress here carries her previous work on emotional shocks into one of the most difficult fields that could well be found. Like every psychiatrist she is familiar with some of the effects of unhappiness in love, but to add to what has already been said on the topic is beyond her powers.

The style of her readable book is less sober than is usual in psychiatry; along with descriptive sections on morbid syndromes and case histories there is critical and largely adverse examination of current psychological theories.

Objective and Experimental Psychiatry. By D. E. CAMERON. New York: Macmillan. 1935. Pp. 271. Price 12s. 6d.

This compilation arose out of the author's distrust of purely descriptive and intuitive concepts of human behaviour. His chapters are brief reviews of some of the American and English publications on disconnected psychiatric topics which have been dealt with experimentally or statistically; methods and findings are discussed. The book lacks the essential qualities of scope and judgment. Investigations published in other languages than English are barely mentioned, discredited work is occasionally reported without the necessary indication of its shortcomings, and in several fields the author shows an unfamiliarity that leads him to omit important studies. In spite of the laudable purpose and outlook set forth in the beginning of the book, it would have been better if less ambitious and more selective.

Zur Genealogie psychopathischer Schwindler und Lügner. VON W. VON BAEYER. Leipzig: Thième. 1935. Pp. 234. Price M. 16.

This study is concerned with the families of sixty-seven psychopaths who had been admitted to the psychiatric clinics of Heidelberg and Munich because of a characteristic tendency to cheat and lie. The incidence of mental disorder of every sort, epilepsy, defect, drunkenness and criminality among their brothers and sisters, parents and cousins is reported in a series of tables and a lengthy text occupying half the monograph. The other half is devoted to detailed case reports of some of the patients, and sketches of their relatives' lives. The author had to cope with great difficulties both in the collection of the material and in its evaluation. He concludes that the patients, although divisible into two main groups, all show the hysterical type of character. He describes them further as "loose" (ungebunden) and inclines to the view that what is inherited in them is a predisposition to this "looseness" in the structure of character: the evidence for this is stated at length.

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PART 2, VOL. 59.

THE MOTOR CORTEX IN MAN IN THE LIGHT OF HUGHLINGS JACKSON'S DOCTRINES.

BY O. FOERSTER (BRESLAU).

The ninth Hughlings Jackson Lecture delivered before the Section of Neurology of the Royal Society of Medicine, on July 31, 1935.

HUGHLINGS JACKSON was the first to point out that there is such a thing as a motor cortex. He was the first to state clearly that the brain, the organ of mind, possesses motor functions. He discovered and elucidated this fact long before further evidence of the motor functions of the cerebral cortex was provided by the experimental investigations of Hitzig and Ferrier on animals. Jackson says: " The convolutions of the brain must contain nervous arrangements representing movements. There is nothing else they can represent except movements and impressions."

He was lead to this conclusion partially by the more general reflection that even the highest nervous centres are only developments of lower centres, which no one doubts represent movements and impressions, a conception in which, as he says, he followed Laycock and Herbert Spencer's doctrine of evolution. But the full evidence of the motor functions of the cerebral cortex was laid bare to him by what he called the experiment made on the brain by disease. That each disease is to be considered as an experiment in the case of man, that it is to be studied anatomically and physiologically, is one of the most important Jacksonian principles, a principle which, at least in Neurology, was not stated nor clearly expressed before his day. He says: " Wherever there is nervous tissue, disease may occur. Now disease can lead to either of two kinds of changes in this tissue, either to destruction of function or to instability, to an over-readiness to discharge. There are destroying lesions and discharging lesions, there is loss of function or over-function. Epileptic convulsions are movements. Although the development of movements occurring during an attack of convulsions be very abrupt and the number of movements developed at once be so great that the visible result is apparently a mere heedless struggle of muscles, epileptic convulsions are movements—caricatured movements. Epileptic convulsions are nothing but occasional abrupt and excessive discharges of motor nerve-cells, of cells the function of which is mediating efferent impulses to muscles. Now in many cases of epileptic convulsions there is a lesion in the cerebral cortex, for instance a tumour, or a syphiloma, or a tuberculoma or a vascular lesion. Whatever may be the pathological nature of such a lesion, the essential cause of the convulsions is the unstable equilibrium of the nerve cells of the cortex. Now as the cortical grey matter responds to those irritating lesions by convulsions, that is to say by movements, the convolutions of the brain must contain nervous arrangements representing movements, the convolutions must possess motor functions."

Nowadays this sounds like a truism. However, before Hughlings Jackson no one had realized it. Jackson's ideas were revolutionary. In his days the prevalent view as to the cause of epilepsy was that it depended upon disturbances of the medulla or the pons, and nobody believed that the cortex of the brain, the organ of mind, contained motor nervous elements and that an epileptic convulsion was nothing but a sudden, rapid and excessive discharge of these cortical motor cells.

Jackson's view was that the whole cortex of the brain contains nervous arrangements representing movements and impressions. But different parts of the brain represent movements and impressions in different ways and in different combinations. He differentiated the *motor cortex proper*, that is to say those cortical areas which are by the way of efferent pathways in direct or indirect connection with the motor nuclei of the spinal cord, from the *superimposed cortical areas*, which, although they contain similar nervous arrangements re-representing movements and impressions, are in connection with the peripheral endorgans *only* by the intermediary of the motor cortex proper. Adapting his terminology to the principle of evolution and to his conception of the hierarchy of the nervous system, Jackson called the motor cortex proper the *middle level* and the superimposed cortical areas *the highest levels.*

I shall not deal in this lecture with the anatomical aspects of the motor cortex, with the specific cyto- and myeloarchitectonic structures of the different areas of which it is composed, and the anatomy of the cortico-spinal pathways. There is one point only to which I must call attention, that is, that Hughlings Jackson had already recognized the existence of the two systems connecting the motor cortex with the spinal anterior horn cells, the direct cortico-spinal pyramidal tract and the many articulate cortico-subcortico-spinal pathways.

Fig. 1 demonstrates the extent of the motor cortex proper of the human brain. It shows the different cortical areas from which motor responses are to be obtained by electrical stimulation. The diagram is the outcome of electrical explorations of almost 300 human brains exposed by operation. In the majority of the cases the exploration was made under local anæsthesia.

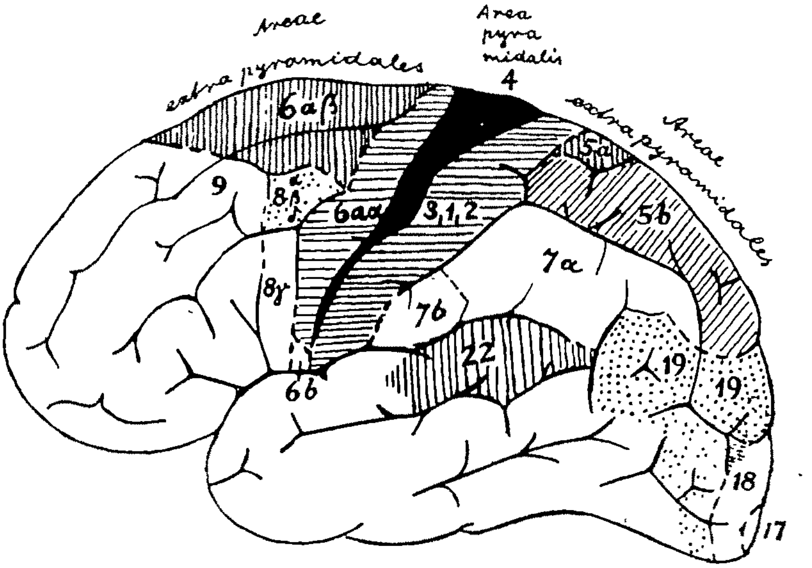

FIG. 1.

In the centre of the motor cortex lies the *anterior central convolution.* It is characterized by two physiological ear-marks, first a low threshold of excitability and secondly its highly differentiated focal subdivisions. In each focus a different part of the body is represented. The stimulation of a given focus produces a single isolated movement of the corresponding part of the body.

The arrangement of the foci in the anterior central convolution from the superior border of the hemisphere down to the Sylvian fissure is well known. At the superior border of the hemisphere the precentral convolution extends to the mesial surface into the paracentral lobule, which contains the foci of the foot, of the toes, of the bladder, and of the rectum.

Nowadays the knowledge of the focal subdivisions of the precentral convolution is common to all neurologists, but Jackson had the same conception as we have to-day. Had he taken a pencil he would have traced the map of the motor cortex with the same accuracy and detailed exactness as it can be done to-day upon the basis of many hundreds of electrical explorations. Jackson did not use the electrical experimental method, he analysed with his keen eyes and his ingenious intuition experiments made by disease on the human brain. He says: "When an epileptic convulsion is limited to the big toe, or to the shoulder, or to the thumb (or to the thumb and the index finger), the seat of the discharging lesion must be different in each of these attacks. In the first case in which the convulsion is limited to the big toe, the discharging lesion must be in that part of the brain in which the big toe is represented preponderatingly. The convulsion limited to the thumb points to the area where the thumb has its main representation.

"When the convulsion begins in the big toe, it spreads secondarily to the foot, next to the calf, then to the upper thigh; the convulsion goes *up* in the leg; thence it spreads to the abdominal wall, to the chest and the shoulder, whence it goes *down* the arm to the fingers, then neck and face follow, first the forehead and the eye-lids, next the lip and the tongue. But when the convulsion begins in the face and spreads to the arm, the fingers are the first to be seized, and the spasm goes *up* in the arm and *down* in the leg, where it terminates in the toes. The part of the body where the convulsion begins indicates the part of the brain where the discharge begins, where the discharging lesion is situated. But from the focus discharging primarily the discharge spreads *laterally* to the adjacent 'healthy' foci. One focus after the other is seized by the radiating waves of impulses. The *march* of the attack, the *order* in which the different parts of the body become involved, reveals the arrangement of the corresponding foci in the precentral convolution."

This principle of localization once being established, one single anatomical observation only was needed. Jackson was provided with it already in 1872. In a case of cortical epilepsy in which all the attacks began in the thumb, and some were limited to it, a tuberculoma of the size of a hazel nut was found just anterior to the precentral convolution in the foot of the third frontal convolution, that is to say just anterior to the focus of the thumb.

All those who read carefully Jackson's descriptions of the march of the convulsions in the case of cortical epilepsy with which he deals, cannot forbear acknowledging that the picture of the focal somatotopic subdivisions of the anterior central convolution stood clearly before his mental eyes long before the experimental work of Hitzig, Ferrier, Horsley, Sherrington and others on monkeys and anthropoids, and the electrical explorations of the human brain undertaken by neurosurgeons as Horsley, Keen and Mills, Hearn Lloyd and Deaver, Parker and Gotch, Sachs and Gerster, Diller and Buchennan, Nancrède, Harvey Cushing, Fedor Krause, van Valkenburg and others had furnished the stones of the mosaic to which the functional subdivisions of the anterior central convolution can be compared. The map of the human motor cortex to be found nowadays in every textbook or handbook of neurology is nothing else but a copy of the picture engraved in Hughlings Jackson's brain.

I shall quote two cases only from my own material to show the localizing value of the onset of the convulsion and the importance of the march of the convulsion, which reveal in detail the grouping of the foci of the precentral convolution.

Case 1.—A coachman, aged 43, fell from the box of his car and hurt his right temple against a stone. He received no concussion or superficial local wound. Within eight days epileptic convulsions occurred, beginning in the mandible, which was opened and deviated to the left, then the tongue was pulled to the left, the corner of the mouth was drawn to the left and both eyelids were closed, the left more strongly than the right. Thereafter the head turned to the left, then the thumb, fingers, hand, forearm, upper arm and the shoulders, first the left shoulder alone, but within the next second the right one also, were involved in succession. Thereafter the muscles of the chest and the abdominal wall of both sides were seized by spasm, then the left hip became involved and the convulsion spread down the leg to the toes and ended by an involuntary emission of urine and fæces without loss of consciousness. Similar attacks followed, each attack as like the others as one egg to another. Operative exposure revealed a cysticercus embedded in the most inferior portion of the anterior central convolution. It was removed without difficulty, and since then the man has been free of attacks.

In the following case the development of the convulsions was in the reverse order:—

Case 2.—A farmer, aged 43, had suffered from epileptic attacks for eight years. The convulsions began in the big toe, but in some of the attacks involuntary urination was the first symptom. From the toes the convulsion spread to the foot, calf, upper thigh, abdominal wall, chest, and the shoulder, and down the arm to the fingers and the thumb. Then the neck, face, tongue, mandible and palate were involved, and the attack terminated by a severe spasm of both vocal cords which almost suffocated the man. After each attack there was a postparoxysmal paralysis of the leg.

In this case I found at operation a small soft tumour in the cingulate gyrus involving to some extent the paracentral lobule. The tumour was removed, and on histological examination was found to be a metastatic hypernephroma. It is noteworthy that a metastatic tumour in the brain may produce serious symptoms over a period of eight years, while the primary tumour causes no symptoms at all. Hypernephromas may live in silence and darkness.

Postparoxysmal paralysis, as occurred in this case, was studied carefully by Jackson. He refers to previous observations of Todd and Robertson on epileptic hemiplegia, but Jackson was the first to give the physiological explanation of the paralysis subsequent to epileptic convulsions, an explanation which has been accepted by all succeeding investigators. The paralysis is due to exhaustion of the cortical motor nerve-cells, and on this depends the transient loss of function.

I cannot deal in this lecture with the many interesting physiological details revealed by the electrical exploration of the anterior central convolution in man. I shall content myself to mention those which were foreseen by Jackson.

The first is the relatively large extent of the finger area, in which each single finger has its special representation. Jackson says: "The quantity of cortical grey matter varies not so much with the size of the muscles of a part of the body, as with the number of movements of that part. Thus the small muscles of the fingers will be represented by much more grey matter in the cortex than will be the voluminous muscles of the upper arm, because the former serve in more numerous, different, and in more specialized movements. Greater differentiation of function implies larger representation in the brain."

The second point is the bilateral cortical representation of different parts of the body. Although inspired by the hypothesis of Broadbent, Hughlings Jackson was the first to realize that not only those muscles which, as a rule, act bilaterally, as the respiratory muscles, the muscles of the abdominal wall, and the muscles of the forehead and the eyelids, have a bihemispherical representation, that is to say, those of the two sides when acting together are represented in each of the two hemispheres, but also that every other muscle group is represented not only in the contralateral hemisphere, but to a certain degree in the ipsilateral hemisphere also. Jackson was led to this conclusion by analysing the march of the convulsions in epileptic attacks which begin unilaterally, but involve at the end of the seizure all parts of the other half of the body as well.

The results of the electrical stimulation of the precentral gyrus in man corroborate strongly Jackson's view. Some foci, for instance those of the larynx and palate, respond even to stimuli of lowest intensity by bilateral effects only; both vocal cords are adducted and the palate is elevated without lateral deviation. When from the focus of the mandible closing of the jaw is obtained, the contractions of the masseters and temporal muscles are equally strong on both sides, but when the mandible is opened it deviates to the contralateral side in consequence of the isolated action of the ipsilateral external pterygoid. The foci of the forehead, of the eyelids, of the shoulder, of the chest and of the abdominal wall respond only unilaterally to threshold stimuli, but the slightest increase of intensity of the stimulus produces bilateral effects. By using stronger stimuli bilateral effects can be obtained from almost any focus, but more easily from the foci of the proximal segments of the extremities than from those of the distal segments. I have observed ipsilateral movements of the fingers in a few cases and only when using very strong faradic currents. According to Jackson the movements of the fingers are the most specialized, the most differentiated, the least automatic movements; they have the least bilateral cortical representation.

It is noteworthy that bilateral effects can still be obtained from the precentral convolution after the corpus callosum has been transected. In several cases of obstructive hydrocephalus in which I divided the corpus callosum for a length of 6 to 7 cm., faradic stimulation of the leg area produced similar bilateral movements of the legs as before operation. These observations confirm admirably Jackson's view that the two halves of the body are represented in each of the two hemispheres.

The third point of interest is the *overlapping* of the foci. It has been assumed that the precentral gyrus is composed of distinct and separate foci, each of which corresponds to a special part of the body *exclusively*, and that each focus in which a single segment of the body is represented contains distinct and separate sub-foci for the different movements of that segment, as flexion, extension, abduction and adduction, but such a formula of extreme localization would never have been accepted by Jackson. He was, as he says, neither a fanatic localizer nor was he a universalizer. According to his doctrines a single part of the body, let us say the thumb, is represented *preponderatingly* in one part of the cortex, but it is represented in other parts of the precentral convolution as well, although in a different degree and in different combinations with other parts of the body. All who have performed many electrical stimulations of the human brain must have become aware of the inconstancy of the effects produced by repeated stimulation of one and the same spot of the precentral gyrus. Let us choose an example. A given spot of the thumb-focus is stimulated repeatedly at intervals of one second by galvanic threshold stimuli. The first, second, third and fourth stimulations result in a movement of the thumb. On the fifth stimulation this movement is fading. The sixth stimulus produces not a movement of the thumb, but a movement of the index finger. The same result is obtained by the seventh stimulus. On the eighth stimulation all fingers except the thumb move. On the ninth stimulation the finger movements are hardly visible. On the tenth and eleventh stimulations the hand moves, and on the twelfth stimulation the primary effect, the movement of the thumb, reappears and is obtained by subsequent stimulations. All these different effects are obtained from one and the same spot and with equal current-intensity. Thus the so-called thumb-focus is not an absolute focus; it contains elements representing the thumb, the fingers and the hand, intermixed with each other. The elements of the thumb are numerically far superior to the other elements and they have the lowest threshold; therefore they are the first to respond to stimulation of the focus. But if the electrical stimulation, which is an un-physiological stimulus, be repeated, the elements of the thumb, after having discharged five to six times, become exhausted and the finger elements lying in the same spot begin to respond. As their threshold is higher than the threshold of the thumb elements, they did not respond to the first stimulus, these are in fact inhibited by simultaneous induction brought about by discharge of the thumb elements. But after the latter have become exhausted the finger elements are in the condition of post-inhibitory exaltation and consequently respond to stimuli previously ineffective. When the finger elements have become exhausted the hand elements, lying in the spot, respond. Finally they become exhausted in their turn. But in the meanwhile the thumb elements have stored up new energy, they have recovered from their exhaustion and have regained their previous reactability.

The inconstancy of the effects and the variation of the responses of one and the same spot to repeated stimulations can be demonstrated in almost every focus of the precentral convolution. Each focus contains not only elements of the part of the body represented preponderatingly in that focus, but also elements of other parts of the body. The foci of the different parts of the body are not like the stones of the mosaic to which they were compared, but they overlap to a more or less considerable degree. The anterior central convolution does not resemble a painting of cubistic style, it reveals rather the intimate mixture of soft colours and smooth forms of a Raphaelitic Madonna.

According to the Jacksonian method of studying the functions of nervous substrata we have not only to regard the phenomena brought about by stimulation of the substratum and the symptoms resulting from its discharge, but we must also take account of the sequels of the destruction of the substratum. In Jacksonian terms we have to analyse the symptoms of discharging lesions and of destroying lesions. The physiological stimulation of the exposed human brain and the physiological experiment made on the human brain by discharging lesions have given us a clear insight into the organization of the precentral convolution; they have revealed its highly differentiated focal somatotopic subdivisions. Do the results of destroying lesions corroborate the conclusions deduced from the results of stimulation and discharge?

Since the classical investigations of Charcot, Nothnagel and many others, cortical crural monoplegia, brachial monoplegia, and monoplegia of face and tongue as the results of destruction of the three main areas of the precentral convolutions are common knowledge. Destroying lesions limited to small parts of the three main areas give rise to paralysis limited to a single segment of the extremities or to a single part of the body. Let me quote a few examples of such local paralysis.

(1) A bilateral traumatic lesion of the paracentral lobules, due to a fragment of shell-casing, produced paralysis limited to both feet and the toes. The movements of the leg and the thigh were not interfered with. There was also loss of voluntary control over the bladder and rectum. Bilateral lesions of the paracentral lobules often give rise to vesical and rectal disturbances.

(2) A tuberculoma of the right paracentral lobule caused paralysis of the left foot and the toes. The movements of leg and thigh were unimpaired.

(3) In a case of cortical epilepsy I excised the leg area and the trunk area. The incision passed just through the focus of the shoulder, and resulted in paralysis of the right leg, of the muscles of the abdominal wall, of the spine and of the chest on the right side, of the right side of the diaphragm and of the right shoulder. The arm, hand and fingers remained free of motor disturbances.

(4) A shell-fragment injured the anterior central convolution 4 cm. below the superior border of the hemisphere. There was paralysis of the right shoulder, the right upper-arm and forearm. The movements of the hand and the fingers were intact, even supination of the hand and opposition of the thumb and all the delicate movements of the fingers, which suffer first and most severely when the hand-finger area is damaged.

(5) In the literature a good many cases of isolated paralysis of the hand and fingers, of the fingers alone, of one or two fingers, or of the thumb alone, are described as the results of small lesions within the cortical finger area. I have seen many similar cases.

(6) In a patient who suffered from Jacksonian epileptic convulsions three small tuberculomas were excised, together with the surrounding brain tissue, from the precentral convolution. The excision was followed by paralysis of the interossei and lumbricales with the typical claw position of the fingers. All the other muscles of the fingers and thumb acted well. I have observed several other cases of similar cortical paralysis of the interossei.

(7) As a result of a traumatic lesion of the most inferior portion of the precentral gyrus, the patient suffered from epileptic convulsions beginning in the tongue and the face. The foci of the larynx, the palate and the mandible were destroyed, and owing to paralysis of the left external pterygoid, the mandible when opened deviated to the left. The movements of the larynx and palate were not affected since they have bilateral representation.

These examples show that small destroying lesions within the precentral gyrus result in paralysis limited to distinct parts of the body. They show just as well as the electrical stimulation and Jacksonian cortical convulsions the differentiated somatotopic subdivisions of the precentral convolution. The character of the cortical paralysis will be analysed later. At the moment I wish only to call attention to the fact that such a focal paralysis is accessible to repair to a considerable degree. The restitution depends on compensation which is furnished, first, by the cortical elements lying in the adjacent unimpaired foci, and secondly by the ipsilateral precentral convolution. The smaller the area destroyed, the more complete the restitution.

According to the anatomical investigations of Campbell, Brodmann, Vogt and Economo, the precentral gyrus of the human brain is composed of two areas of different cyto- and myeloarchitectonic structure, of Area 4 or the area giganto-pyramidalis, and Area 6 a*a* or the area agranularis centralis. The extent of Area 4, which is marked black in fig. 1, is characterized by the presence of the Betz cells in the fifth cell layer. The size of the Betz cells diminishes gradually in the descending direction. This fact, well known to-day, was foreboded by Jackson. In a paper published in 1874 he says: "I should, for theoretical reasons, expect that of the centres those which represent movements of the small muscles (eyes, face, fingers, hand) will have cells comparatively small, smaller than the cells superintending movements of the large, more voluminous muscles of the limbs and the trunk." A few years later, in 1879, Jackson's opinion was confirmed by the anatomical researches of Bevan Lewis.

We come now to the question as to whether there are physiological differences between the two areas composing the precentral gyrus in man, Area 4 and Area 6 a*a*. The opinion has been recently expressed that the different cyto- and myeloarchitectonic structure of these areas were merely anatomical details without physiological significance. Hughlings Jackson was of other opinion. He says:—

"Differentiation of function implies differentiation of structure and differentiation of structure means differentiation of function. So far as the comparative anatomist detects homological cerebral structures, so far, it is to be hoped, will the physiologist be able to develop the homological *functions*, and so far as the anatomist ascertains *different structures*, so far will the physiologist be able to detect different functions. Since, as Lockhart Clarke has pointed out, the structure of the anterior convolutions does differ from the posterior, they must serve differently in mind."

Physiologists have attempted to analyse the functional differences of Area 4 and Area 6. I refer to the fundamental work of the Vogts and of John Fulton and his school. In man Area 4 and Area 6a*a* differ from each other by their threshold of excitability. Both areas respond to electrical stimulation by the isolated movements of a part of the body or of a single segment of the extremities. But to obtain these effects from Area 6a*a* a considerably stronger stimulus is needed than in Area 4. The difference of the threshold amounts to 1 to 2 ma. Under general narcosis Area 6a*a* becomes inexcitable to the galvanic current, and under deep narcosis even to faradic currents. Area 4 preserves its excitability under these circumstances.

As Vogt has demonstrated, the isolated movements obtained from Area 6 a*a* do not depend on motor impulses mediated by the direct efferent tract of Area 6, but on impulses transmitted from Area 6 to Area 4 by the superficial cortical cell layers. From Area 4 the impulses are conveyed to the muscles by the pyramidal tract. After excision of Area 4, or after transection of the superficial cortical layers of Area 6, isolated movements are no longer obtained by electrical stimulation of Area 6. This can be demonstrated in man. When Area 4 is excised, or when the pyramidal tract is interrupted, electrical stimulation of Area 6a*a* fails to produce isolated movements. When the superficial cortical layers of Area 6a*a* are cauterized by electro-coagulation, isolated movements are no longer obtainable from Area 6a*a*, but they can be produced promptly by stimulation of Area 4.

If Area 4 be excised, or the pyramidal tract be interrupted, Area 6a*a* still responds to strong faradic stimuli, not however by isolated movements, but by mass movements of the whole contralateral half of the body, which I shall describe later when dealing with Area 6aβ. These complex movements depend on impulses originating in Area 6aα and mediated by its own efferent pathway to the subcortical centres, and through them to the spinal motor nuclei.

We come now to the *postcentral convolution*. It is the main cortical area of sensibility. Of this fact Jackson was well aware, though he never believed that any area of the cortex was purely motor or purely sensory. Each cortical area represents movements and impressions, one area preponderately movements, another preponderately impressions. The precentral areas are chiefly motor, the postcentral convolution is chiefly sensory. The exactness of this Jacksonian statement can be demonstrated beautifully by electrical stimulation of the human retrocentral convolution under local anæsthesia. Galvanic currents produce the same isolated movements as are obtained from the precentral convolution, but the threshold is considerably higher; the difference amounts to 2 to 4 ma. Under general narcosis the galvanic currents fail to produce motor effects, and if the narcosis be deep even strong faradic currents are ineffective.

The isolated movements obtained from the postcentral convolution are brought about by the intermediary of Area 4. The impulses are transmitted from the postcentral gyrus to Area 4 by the U-fibres connecting both central convolutions. If Area 4 be excised or the pyramidal tract be interrupted, the retrocentral gyrus no longer responds with isolated movements. Under these circumstances strong faradic stimuli produce mass movements of the whole contralateral half of the body similar to those obtained from Area 6aα when the pyramidal tract is interrupted. They will be described later.

As has been said, the postcentral convolution is the main cortical sensory area. It is composed of highly differentiated foci in which the different parts of the body have their sensory representation. In the posterior part of the paracentral lobule, the structure of which is homologous to that of the postcentral gyrus, the bladder and rectum are represented. Then follow the sensory foci of the different parts of the body from the toes up to the head. Faradic stimulation of any focus is attended by a sensation in the corresponding part of the body. (Galvanic stimuli are ineffective.)

The epileptic attacks resulting from discharge of the postcentral convolution are characterized by sensory auræ. The "subjective sensation," to speak in Jacksonian terms, begins in that part of the body which is represented in the focus which discharges primarily. From the part where it begins the sensation spreads like a wave successively to the other parts of the body in the order corresponding to the grouping of the foci in the postcentral convolution. The discharge may be limited to the sensory elements so that the epileptic attack consists in subjective sensations only. But as a rule the sensory aura is followed by motor discharges which show the same march as do the convulsions originating from the precentral gyrus. All these details were well known to Hughlings Jackson. He describes beautifully the warning, the crude sensations, the feeling of numbness, of tingling, or of pain. He explains them as being mental states attending the discharge of the cortical sensory elements. With a simply astonishing exactness he described in 1863 the order of the spread of the subjective sensations in a case of cortical sensory epilepsy. Another detail often to be observed in postcentral epileptic attacks, was also mentioned by him; the first sign of the motor discharge following the sensory aura may be a long lasting tremor preceding the clonic twitching.

A few of my own observations will illustrate these points.

Case 3.—As a result of a fragment of shell embedded in the posterior part of the paracentral lobule the patient suffered from sensory epileptic fits beginning with a sudden feeling of micturition and tenesmus, followed by a wave of burning and tingling sensations which spread from the toes up to the face and into the buccal cavity. The sensation terminated in the larynx by a convulsive cough. Some of the attacks remained purely sensory, but in the majority the sensory aura was followed by motor convulsions.

Case 4.—A patient with a traumatic lesion of the postcentral convolution involving foci of the fifth and fourth finger suffered from epileptic attacks beginning with a sensory aura in the fingers, which spread over the whole half of the body. The aura was of long duration; the motor discharge which followed was relatively short and often limited to the arm. After each attack there was a complete postparoxysmal hemianæsthesia, a typical example of exhaustion of the postcentral gyrus caused by the preceding long-lasting discharge of the sensory elements.

The last case is interesting from still another aspect. The patient had a traumatic scar in the left fourth finger. By pressure upon the scar the attack could be produced with experimental promptness. I have observed several other cases of the same kind. They belong in the group of reflex-epilepsy, the mechanism of which has been explained in a masterly fashion by Jackson. He describes a patient who cut the palmar surface of his left index finger with a gouge and who nine months later developed epileptic convulsions always beginning in the left index and middle fingers. Jackson says: "It may be supposed then that in such cases of convulsion there are two factors: (1) a part of the nervous system unstable, and (2) an irritation starting from the finger, which travels to the cortical area being in the condition of unstable equilibrium and then determines the unstable cortical grey matter to discharge. The irritation from the injured finger acts on the cortex only as the explosion of a gun cap does on the charge in the barrel."

According to Jackson the sensory aura of epileptic attacks depends on the discharge of cortical sensory cells. The aura is in itself an epileptic fit. He says: "It is worth mentioning that some patients have a feeling as if a part were convulsed when it does not really move. One of my patients subject to veritable convulsions beginning in the left thumb had sometimes what he called convulsions not to be seen of that part. Another patient had the feeling of convulsion of one side of his face, but looking in a glass he saw that it did not move. No doubt that, if a man, subject to fits beginning in his right thumb, were to lose the right arm by amputation, his fits would still seem to him to begin in his spectral thumb, for some time at least."

Jefferson has recently described such a case which amounts to the experiment referred to by Jackson. A lady who suffered from local sensory fits of painful character, always beginning in the fingers, was advised to have the nerves of the arm injected with alcohol. Had she looked heavenward she would have seen the earnest smile of the father of Neurology, lifting his finger to warn her, but unfortunately the patient did not do so, she accepted the suggestion given to her. What happened exactly is unknown, but the arm became black after the injection and was amputated above the elbow. The sensory fits were entirely and completely unchanged. I have observed a similar case to which I referred briefly some years ago.

We come now to the frontal extrapyramidal Area 6aβ. When this area is stimulated under local anæsthesia by strong faradic currents a complex mass-movement of all parts of the contralateral half of the body is obtained. Head, eyes and trunk are turned to the contralateral side and the contralateral arm and leg execute combined movements. As a rule the arm is raised and abducted, the forearm is flexed, the hand is pronated and the fist is closed or opened. I call this compound movement the flexor synergy of the arm. Less frequently the reverse synergy ensues, the arm is adducted and extended, but the hand is pronated as it is in flexor synergy. The leg is simultaneously flexed at the hip and knee with dorsal flexion of the foot and toes, constituting a flexor synergy of the leg; or there may be extension of hip and knee and plantar flexion of the foot, an extensor-synergy of the leg.

The motor effects obtained from Area 6aβ depend on the proper efferent tract of this area which mediates the impulses to the subcortical centres and through them to the spinal cord and the muscles. When the precentral convolution is destroyed or the pyramidal tract is interrupted, stimulation of Area 6 aβ produces the same compound effects as are obtained if the precentral convolution be intact.

Epileptic convulsions originating from Area 6aβ have a characteristic aspect. There is no sensory aura: all the muscles of the contralateral half of the body are thrown into spasm almost at once; the head, eyes and trunk are turned to the side opposite to the discharging lesion and the arm and leg are involved in tonic-clonic mass-convulsions; in the arm the flexor synergy generally predominates, while in the leg the extensor synergists prevail. Towards the end of the discharge the flexor and extensor synergies alternate with each other by typical clonic spasms. In some cases the convulsions of the muscles of the spine are so violent that the patient, if standing when the attack starts, rotates two or three times around himself and then falls to the side opposite to the discharging lesion. Several times I have seen a patient, if lying in bed, thrown out of it by the convulsion and rolled over to one side.

The motor effects of stimulation of the *superior parietal lobe, Area* 5, are very similar to those obtained from Area 6aβ. The main difference is that on stimulation of Area 5 the ipsilateral extremities, chiefly the leg, take part in the reaction soon after the onset of the spasms in the contralateral extremities.

The superior parietal lobe is a part of the sensory cortex, but unlike the retrocentral convolution it is not subdivided into separately differentiated sensory foci. The whole contralateral half of the body is represented as an entity, and there is representation of the ipsilateral half as well, although to a smaller degree. Faradic stimulation of the superior parietal lobe evokes a sensation which is localized over the whole contralateral half of the body, and if the stimulation be prolonged the sensation spreads over the ipsilateral half. The paræsthesiæ are often painful. Some of my patients complained of intestinal pain, of an epigastric sensation, or of pain similar to that of angina pectoris.

Stimulation of the superior lip of the interparietal sulcus evokes violent vertigo. The patient sees the objects before him moving towards the side of stimulation, or he has the sensation of turning towards the contralateral side, although objectively nothing happens and no turning of the head and the trunk really occurs.

In conformity with the sensory-motor functions of Area 5, the epileptic attacks originating from it begin with a sensory aura. Usually a wave of paræsthesia shoots over the contralateral half of the body and radiates soon to the ipsilateral half. In some cases the patient complains of violent gastric pain, and in several of my cases the warning was a sudden attack of vertigo. The motor discharge following the premonitory aura leads to combined flexion of the contralateral arm and leg and rotation of the head and the eyes. A little later the ipsilateral leg is drawn up and then the ipsilateral arm.

The following case is of special interest in this connection:—

Case 5.—A girl, aged 17, when 2 years old had an attack of infantile hemiplegia, which cleared up completely. When 14 years old she began to suffer from epileptic attacks. In each fit the warning was an attack of vertigo; it seemed to her as if objects moved to the left side, after which she had the feeling of being rolled over to the right side. The vertigo was of long duration and was often accompanied by violent nausea. The subsequent motor discharge was of the character described above. I exposed the left parietal lobe and found a large cyst in the interparietal fissure and at the bottom of the cyst a sclerotic scar. Faradic stimulation of the superior lip of the fissure evoked vertigo similar to that of her spontaneous fits. The girl cried aloud: "Hold me, I fall from the table, to the right side." Objectively nothing happened. The same feeling of vertigo was called forth during the excision of the scar. Since the operation, seven years ago, the patient has been entirely free from attacks.

Jackson has repeatedly discussed vertigo as a common warning in epileptic fits. They are among his most luminous dissertations, and I regret that for reason of time I cannot enter upon them in this lecture.

The temporal extrapyramidal area, Area 22, responds to faradic stimulation by the same compound movements as Area 6$a\beta$. The sensory effects evoked by stimulation of the temporal lobe are chiefly acoustic sensations; the patient hears noises, thunder roaring, buzzing, whistling, sometimes voices of obscure character, seldom real words. Penfield describes dizzy feelings and a sensation about the heart on stimulation of the external surface of the temporal lobe. The epileptic attacks originating from the temporal lobe often begin with an acoustic aura.

I shall quote one case only:—

Case 6.—A boy, aged 11, with right-sided hemiplegia resulting from birth injury to the brain, suffered from epileptic attacks, the warning of which was an acoustic aura. He heard a confused din of voices, sometimes real words, for instance: "Boy come along!" The aura was followed by violent convulsions, in which his head, eyes and trunk were turned to the right, and his right arm and leg were drawn up by tonic-clonic mass convulsions. In some of the attacks the boy rolled over to the right side. The most interesting point in this case was that the attacks were provoked with experimental promptness by a sudden noise, chiefly when it was unexpected; for instance, when the door was opened abruptly or when an object fell upon the floor, or when the boy was called by somebody whom he had not seen. The case is a typical example of acoustic reflex epilepsy. The two factors to which Jackson directed attention are evident in this case: (1) An area of cortex in the condition of highly unstable equilibrium; (2) incoming impulses which act on the unstable cortical area as the explosion of a gun cap does on the charge in the barrel. Faradic stimulation of the first temporal convolution produced an epileptic attack which was of the same character as the spontaneous attacks, including the acoustic aura.

I pass over the cortical area, 6b, the so-called masticatory area, and the oculomotor cortical areas, 8 and 19, the frontal and occipital motor eye-fields.

DESTRUCTIVE LESIONS OF THE MOTOR CORTEX.

If movements are represented in the cortical motor areas it is obvious that destruction of those areas must result in loss of movements, and that destruction of a single area must lead to loss of the special movements represented in that area. As a concrete example the immediate sequelæ of operative excision of the leg area of the precentral convolution are: (1) Total loss of voluntary motility of the contralateral leg; (2) impairment or loss of reflex activity as well. The stretch reflex is abolished, the paralysis is flaccid. The knee-jerk and ankle-jerk were lost in my cases and no plantar response was obtainable. The latter reflex was the first to reappear, within five to ten hours. In every case the plantar response was then extensor. The tendon reflexes returned within two to three days, the stretch reflex proper within eight to ten days. Then the stage of loss of reflex activity merged gradually into the subsequent state of increased reflex activity; the paralysis became spastic.

The increased reflex activity depends on the loss of control exerted by the higher levels upon the lower levels. The cortical motor leg area is provided not only with innervatory elements, which, if active, bring about contraction of muscles, but also with inhibitory elements which control the reflex activity of the spinal cord. If this inhibitory function of the cortex be lost the spinal cord behaves like a horse which, no longer checked by the bridle, rushes away on a touch of the spur. I fully realize that many arguments have been put forward against this theory, but no one has given a better explanation of reflex over-activity than Hughlings Jackson did by his principle of loss of control.

The immediate result of excision of the cortical leg area is an initial total loss of voluntary motility of the leg. At the first glance this is surprising, as the leg is represented not only in the area excised, but also in many other cortical areas. Why then is the paralysis total? All the different cortical motor areas, the precentral, frontal, postcentral, parietal and temporal, represent a co-operative society, each partner of which contributes a specific, more or less important, quota to the validity of the society (in the case we deal with, to the achievement of voluntary movements). If one partner, especially if such an important partner as the anterior central area, be eliminated abruptly the whole co-operative society becomes functionally impotent in spite of the anatomical integrity of the other partners (in this case the extra-pyramidal cortical areas). But this initial inactivity of the co-operative society is transitory, for sooner or later a re-organization of the surviving members—of the cortical motor areas left intact—takes place. They regain their functional capacity and thereby voluntary motility is re-established. But the restitution of motility is not complete. As Jackson has pointed out, the movements of a limb are represented in many different cortical areas, but in each area in a different degree and in different combinations with other limbs. The specific function of Area 4 is the isolated innervation of single muscle groups. The isolated movements of the single segments of the leg are represented in no other cortical area. Therefore the isolated movements of the toes, of the foot, of the leg and of the thigh are abolished by destruction of the leg area in the precentral convolution. The mode of representation of the leg movements in the other cortical areas, the extrapyramidal areas, greatly differs from the representation in the anterior central convolution. The leg movements brought about by the activity of the extrapyramidal areas are compound movements of all segments of the leg, stereotyped synergies, as the flexor synergy and the extensor synergy. As we have seen, these synergies are elicited by electrical stimulation of the extrapyramidal areas, they appear as caricatured mass movements in the convulsions originating from those areas, and we now see that they are the movements which are performed voluntarily by the patient after the leg area in the precentral convolution has been excised. These synergies are the sole movements which can be performed.

These synergies are unmodifiable, one component being coupled inseparably with the other components. When the patient dorsiflexes his foot, this movement is accompanied by a simultaneous flexion of the knee and the hip. When he flexes his leg, the thigh is flexed and the foot is dorsiflexed. When the leg is raised the knee is flexed and the foot dorsiflexed. Vice-versa voluntary extension of one of the three segments of the leg is associated with extension of the other two.

The restitution of voluntary motility of the leg after its initial total abolition is called by Jackson *compensation*. According to him a nervous substratum which is active in the compensation can only develop functions primarily immanent to it, it can contribute only to the achievement of movements to which it had already contributed under normal conditions; it can contribute to compensation by its specific functions only.

In the case we deal with, that is excision of the motor precentral leg area, compensation depends not only on the extrapyramidal motor areas of the corresponding hemisphere, but also on the leg area of the other hemisphere. It is, I believe, one of Jackson's greatest achievements that he pointed out that more or less all muscle groups of one half of the body are represented in both the contralateral and ipsilateral hemispheres, although to a different degree. Muscles acting chiefly bilaterally, as those of the abdominal wall, of the spine and the chest, of the eyelids and of the mandible, have the most pronounced bi-hemispherical representation. The proximal muscles of the extremities have a greater bilateral representation than the distal muscles.

As soon as the ipsilateral precentral leg area and its efferent tract, the uncrossed pyramidal tract, take part in the compensation, the possibility of innervating single muscle groups is restored, and thereby the stereotyped extrapyramidal synergies, unmodifiable at first, may undergo modification. One component of the synergy can be accentuated relatively to the other components by isolated impulses to the corresponding muscle group. For example, on raising the leg the associated movements of the leg and the foot, although still present, recede into the background. The further the compensatory function of the ipsilateral leg area progresses, the more the ability to perform isolated movements of the single segments of the leg is re-established. But Jackson says: "Compensation is never complete." When the patient who has reached the degree of compensation described attempts to perform an isolated movement of a single segment of the leg against external resistance, the synergy breaks through immediately. In order to surmount external resistance stronger cortical impulses are needed, and as they cannot be furnished by the ipsilateral leg area alone, the co-operation by the extrapyramidal areas is indispensable.

In bilateral lesions of the leg area the compensation by the ipsilateral leg area fails; the only voluntary movements possible are those of the extrapyramidal synergies. Isolated movements of the single segments of the leg are permanently lost.

The motor disturbances resulting from excision or destruction of the arm-area are analogous to the disturbances of motility of the leg. There is an initial total loss of voluntary movement and of reflex activity of the arm; the paralysis is flaccid. Then the reflexes return and become increased as the paralysis becomes spastic. The restitution of voluntary motility of the arm develops as in the leg. The isolated movements of its segments remain absent, but compound movements represented in the extrapyramidal areas are possible, as the *flexor synergy*, consisting in abduction of the upper arm, flexion of the forearm, pronation of the hand and closing or opening of the fist, and the *extensor synergy* composed of adduction of the upper arm, extension of the forearm, pronation of the hand and closing (or opening) of the fingers. The synergies are unmodifiable, one component is coupled inseparably with the other components. If the arm be raised the forearm is flexed and the hand is pronated at the same time. If the forearm be flexed the upper arm is raised and the hand is pronated. There is a noteworthy similarity between these compound movements performed voluntarily by the patient and the synergies produced by electrical stimulation or by an epileptic discharge of the extrapyramidal cortical areas. Similarly, the components of the extensor synergy are inseparable; if the forearm be extended, the arm is adducted and the hand is pronated; if the arm be adducted, the forearm is extended and the hand is pronated. When later the ipsilateral arm area takes part in compensation and isolated impulses can be forwarded to single muscle groups, the synergies can be modified, one component can be accentuated relatively to the other components; for instance, the arm can be raised to a considerable degree without the forearm being flexed, or the forearm may be flexed without the arm being abducted at the same time.

But even if compensation by the ipsilateral arm area has reached a high degree, the specialized movements of the fingers almost always remain impaired, because they are represented almost exclusively in the contralateral finger area. The patient can close and open his fist, but he cannot flex a single finger without the other fingers and the thumb being flexed at the same time. On attempting to extend one finger all the others extend. Moreover, he cannot bend a single segment of a finger: for instance, the terminal phalanx of the thumb or the middle phalanx of the index; when he attempts to do so all the fingers and the thumb flex at all joints. Opposition of the thumb to the other fingers is lost; when the patient tries to execute this movement the fist closes. Consequently all the finer skilled movements of the fingers, as buttoning, writing, painting and drawing are lost. Every case of excision or destruction of the cortical hand-finger area illustrates the validity of Jackson's principle of Dissolution. The less specialized gross movements, such as closing and opening the fist, are little or not at all impaired; the skilled, most specialized movements of the fingers, representing the specific functions of the human hand, are profoundly disturbed. They are the first to suffer when a destroying lesion begins to damage the cortical finger area, and they are the last to recover when the pathological process is removed or when compensation develops.

Nevertheless it must be said that in some cases of destruction of the arm-finger area even the finer skilled movements of the fingers may be restored by the compensatory function of the ipsilateral finger area, especially under the influence of systematic treatment by exercises.

The following case is a good example :—

Case 7.—When I first saw the patient the only movements he could perform were the stereotyped extrapyramidal synergies of the arm. Under treatment he soon learned to modify them by the compensatory function of the ipsilateral arm area to such a degree that he could raise the arm without bending the forearm and open and close the fist strongly, but the finer skilled movements of the fingers remained absent. For instance, in order to hold a pencil, he had to grasp it in his fist. After treatment had been continued for three years the patient learned to perform isolated movements of the fingers and thumb; opposition of the thumb became perfect, he was able to hold a pencil correctly, his handwriting became, although not calligraphic, much better than that of many normal individuals. A post-mortem examination showed complete degeneration of the left pyramidal tract in the medulla.

Case 8.—Another case was that of a boy who suffered from cortical epileptic attacks, resulting from a sclerotic scar, due to infantile encephalitis. The whole cortical hand-finger area was excised and the epileptic convulsions ceased. There was at first a total loss of all voluntary movement of the hand and the fingers, but the boy soon regained gross movements, as closing and opening his fist, but the more specialized skilled movements of the fingers could not be performed. For instance, when he attempted to oppose the thumb, all the fingers and the thumb flexed. Under treatment by exercises, continued for years, the skilled movements of the fingers also were restored. He learned to oppose his thumb in a perfectly correct way, but this movement was accompanied by a similar movement of his right thumb; the latter constitutes direct evidence of the compensatory activity of the left cortical finger area. All the finer skilled movements of the fingers, as buttoning and writing, were also accompanied by homologous movements of the left hand, and these associated movements never disappeared completely.

Time compels me to pass over the motor disturbances resulting from excision or destruction of the cortical trunk area and the areas of the face, tongue and mandible, although a description of these disturbances would show in a particularly clear light the amazing gift of observation possessed by Hughlings Jackson.

Summing up the motor disturbances resulting from destruction of the anterior central convolution, we can say that the main symptoms are :—

(1) The *negative* symptoms are loss of the isolated innervations of single muscle groups, loss of the most specialized movements, and loss of the faculty of modifying the stereotyped extrapyramidal synergies and of adjusting them to special purposive acts. The loss of function can be compensated to a more or less considerable degree by the ipsilateral precentral gyrus.

(2) The *positive* symptoms are: (*a*) Exhibition of the functions of the intact extrapyramidal cortical motor areas which are no longer under the control of the anterior central convolution and are dissociated from its activity; (*b*) increased spinal reflex activity, the spinal reflex machinery being freed from the control exerted upon it by the anterior central convolution.

We have to consider now the results of destructive lesions of the *extrapyramidal* cortical areas.

Excision of Area 6aβ or 22, which I have performed in about forty cases, either gives rise to no detectable symptoms, or, if there are symptoms at first, they disappear very soon. The initial symptoms which were observed in some of these cases will be described in a later communication, but I may say that in no case were forced grasping or the slightest degree of spasticity observed.

That after excision of Area 6aβ or Area 22, motor disturbances are absent or, if at first present, disappeared within a short time, is surprising.

Both areas certainly possess important motor functions as has been demonstrated by electrical stimulation and by the epileptic convulsions originating from them. Yet destruction of the areas leads either to no detectable disturbances, or to slight and transient disturbances only. The apparent discrepancy is one of the problems discussed and elucidated by Jackson in many of his papers. When the cortical area in which movements are represented discharges, movements are produced, and if the discharge be a sudden violent outburst of excessive impulses convulsions are brought about. But when the same area is put out of function by a destroying lesion, no detectable motor deficiency is to be expected, if the movements represented in the destroyed area be represented in the same, or in approximately the same, combination and order in other cortical areas also. Under such circumstances the loss of function of the destroyed area is compensated by the other areas. Now Area 6aβ, the postcentral area, Area 5 and Area 22 are functionally very much alike. When Area 6aβ is destroyed there are still other extrapyramidal areas available for compensation. The same principle holds good for Area 22. It does not apply to the retrocentral areas, the postcentral gyrus and the superior parietal lobe, which are the main cortical sensory areas; their destruction leads not only to loss of sensibility, but also to motor disturbances due to loss of afferent impulses indispensable for the regulation of efferent cortical impulses. The motor disturbance brought about by lesions of the sensory cortical areas is an ataxia, equivalent to that produced by lesions of the posterior spinal nerve roots or other afferent tracts.

The important part which the extrapyramidal areas play in the performance of movements is best demonstrated by cases with destructive lesions of the precentral convolution in which motility has been greatly improved by the compensatory function of the extrapyramidal areas and in which later, for some reason or another, the functions of these also become impaired.

In one of my cases of traumatic injury of the anterior and posterior central convolutions the initial complete hemiplegia had improved greatly. The patient suffered from epileptic attacks originating from Area 6aβ. After operative excision of this area the patient had a complete hemiplegia, first flaccid, later spastic. Voluntary motility returned, but the high degree of compensation reached before operation was never attained.

Another patient with a large traumatic lesion of the brain involving the central convolutions and the frontal extrapyramidal Area 6aβ, had a severe right-sided hemiplegia. He could, however, perform the flexor and extensor synergies fairly well. As he suffered from epileptic convulsions originating from the parietal Area 5, I excised that area to its full extent. Although the complete hemiplegia which followed the operation underwent a certain recovery, the motor disturbance remained much more marked than it had previously been. The only extrapyramidal area left intact, Area 22, did not contribute much to the restitution of motility.

Reviewing experiences collected from many hundreds of cases of destruction of the cortical motor areas I can say that the more extensive the lesion, the more severe is the paralysis and the fewer the movements which persist. Jackson has described in a masterly manner the different degrees of hemiplegia and has shown how they can be explained by the the principle of dissolution. The most specialized, most voluntary and least automatic movements are the first to suffer and the last to be restored. The greater the number of areas destroyed in addition to the precentral convolution, the more the movements which are least specialized, least voluntary and most automatic, are involved.

But even if the whole motor cortex of one hemisphere be destroyed there is still the other hemisphere available for compensation. Jackson's view of the bilateral cortical representation of each half of the body, proved to be correct by many observations already referred to, receives further corroboration from cases of congenital or early acquired destructive lesions. Though such lesions may involve the whole motor cortex of one hemisphere, an astonishing degree of motor ability may exist. If the whole motor cortex be destroyed in adults motility is recoverable to a much smaller degree.

The last question to be discussed is the differentiation between Area 4 and Area 6a. The precentral convolution in man is composed of two areas anatomically different, Area 4 and Area 6aα. These two areas behave differently when stimulated by the electric current. The question therefore arises as to whether the motor disturbances resulting from isolated destruction of one of these areas differ from those due to destruction of the other. The Area 4-syndrome and the Area 6-syndrome have been carefully analysed in monkeys and anthropoids by John Fulton and his school. In human pathology cases suitable for the analysis of this problem are extremely rare. In one case of excision of the leg area, strictly limited to Area 4, I found the same motor disturbance as those which follow excision of the whole leg area in the precentral convolution, that is to say both Area 4 and Area 6aα.

In a second case in which the excision was limited to the foot centre in Area 4, the foot and the toes were completely paralysed at first, the paralysis was flaccid and the Achilles and the plantar reflexes were absent. Four hours after operation an extensor response of the toes could be elicited, and eight hours after operation the Achilles reflex returned. Then ankle clonus and Rossolimo's sign developed, and movements of the foot occurred in association with flexion or extension of the other segments of the limb, but isolated movements of the foot and the toes could not be performed. In walking the foot as well as the leg and thigh were flexed and the toes did not drop or scrape the ground. After treatment by exercise the patient learned to dorsiflex and plantarflex the foot independently of flexion and extension of the other segments of the limb, provided that the muscles did not have to overcome external resistance, but the isolated movements of the toes were lost permanently.

So far as conclusions can be drawn from these two observations, they seem to demonstrate that the motor disturbance resulting from isolated destruction of Area 4 in man does not differ to a detectable degree from that due to destruction of both Areas 4 and 6a*α*.

I have no cases of excision or destruction strictly limited to the arm and the finger areas. In this region of the precentral convolution Area 4 lies mainly or exclusively in the depth of the Rolandic sulcus. Excision of the whole Area 6a, that is to say Areas 6a*α* and 6a*β*, without interference with Area 4, has not been described in man.

Perhaps one of the most ingenious conceptions of Hughlings Jackson is his doctrine that the whole cortex of the brain, the highest levels as well as the middle levels, contain nervous arrangements representing movement and impressions, but unfortunately time will not permit me to deal with this subject.

In this lecture I have covered only a small part of neurology, yet I believe that I have demonstrated that in this field all the pioneer-work was done by Hughlings Jackson. The doctrines he developed have been, and will be for ever, a guide-post for subsequent research. But there is no other field of neurology with which Hughlings Jackson was not equally familiar. There is scarcely a single neurological problem which was not illuminated and elucidated by his prophetic ingenuity. Jackson's writings are the Bible of Neurology, the canon for the votaries of our science.

THE INFLUENCE OF EXPERIMENTAL LESIONS OF THE SPINAL CORD UPON THE KNEE-JERK.

II—CHRONIC LESIONS.

WITH AN APPENDIX "A NOTE ON THE 'SPINAL' AND 'DECEREBRATE' TYPE OF KNEE-JERK IN THE CAT."

BY E. G. T. LIDDELL.
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USING the inhibitability of the knee-jerk as a criterion of "spinal shock," Fulton, Liddell and Rioch [9, 10, 11] showed that a vulnerable area of the spinal cord is the ventrolateral. They found that a lesion in that area was followed by increase in susceptibility of the jerk to inhibitory stimuli, which was well marked but somewhat less in degree than that produced by total section of the cord. And they concluded that severance of the descending vestibulo-spinal tract was the essential factor in lowering the resistance of the jerk to inhibitory stimuli [11, 12]. Similar results were obtained by a lesion of the medulla in the region of the vestibular nucleus [12].

Since their observations were made only after acute lesions of the cord, it became of interest to observe the state of "shock" some time after the lesion, or, in other words, to inquire into the progress of the spinal centres after withdrawal of the fringe of excitation from the vestibule and mid-brain, and to find out how soon recovery or compensation develops. Observations have already been published upon the recovery of isolated spinal centres after complete transection of the cord [19].

Preparatory operation.—The operations were performed with full aseptic precautions, Nembutal intraperitoneally being the anæsthetic. Small young cats were used, their weight averaging 2 to 3 kg. In all fifty preparations were made and examined. After laminectomy about the level of the last rib and exposure of two roots, the cord was laid bare more ventrally on one side by resecting bone, so that, when rotated slightly by holding the dura in mouse-tooth forceps at a point midway between the roots, the ventral spinal vessels came into view. Up to this stage care had been taken not to perforate the dura, especially dorsally, since in earlier experiments it was found that removal of the dura and the slightest injury of the dorsal roots gave rise to a massive scar containing nerve-roots and muscle, with subsequent degenerations in the dorsal columns.

In order to avoid this gross scar in making ventrolateral lesions, the cord was gently rotated by holding the dura, as just described, until the ventral vessels became visible. A Graefe knife or fine scissors was then employed to pierce the dura latero-ventrally and sever the subjacent cord to the desired extent. It was not difficult to gauge the exact place and depth of the lesion, and, having the ventral vessel as a guide, to avoid transgressing the midline (fig. 1). No attempt was made to close the dural opening. The spinal muscles, deep fascia and skin were afterwards sutured in layers. Immediately after the operation and before recovery from the anæsthetic the knee-jerk on the side of the lesion was found to be slow in rise and fall, and the leg tended to swing back and forth after the fall. On the other side, the jerk was quicker, without subsequent oscillations.

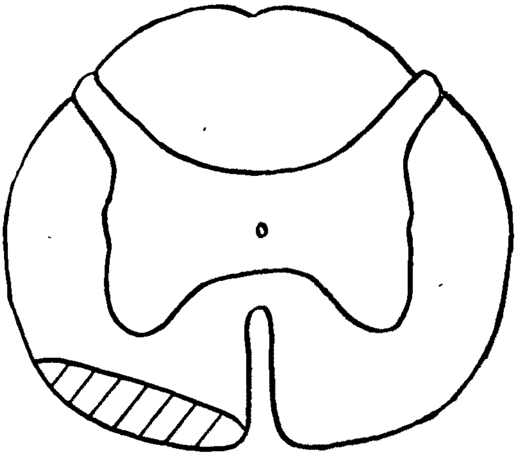


FIG. 1.—Diagram to show approximate area and extent of the ventrolateral lesions.

Post-operative progress.—On the day following the operation and for some days subsequently it was common to observe weakness in both posterior limbs, together with distension of the bladder and overflow. This condition was probably due to transient œdema of the cord because, after a few days, the animal recovered and became able to walk, and about the same time the bladder began to empty normally. This post-operative paraplegia was more transient when the lesion was made by a knife rather than by scissors. Fulton and Keller have also preferred the ophthalmological knife to scissors [14]. When voluntary movement is re-established and the animal held up by the scruff of the neck, the leg on the operated side is seen, at rest, to be limply dependent in an attitude of slight flexion. Although some patience is needed to examine such a non-co-operating subject as a cat with good voluntary power, it is possible to observe that to passive flexion imposed by the palm of the hand placed under the pad, the limb feels flaccid, or partly so, on the side of the lesion. But on the unoperated side the limb's posture is one of semiflexion, as in normal animals when held up by the neck, and the limb feels more resistant to passive flexion [29]. The knee-jerk on the operated side is more "spinal," that is to say, its rise and fall seem slow, but the movement is ample and the leg swings back and forth afterwards.

Later post-operative progress.—Within about two weeks of the operation an interesting change began to declare itself in the limb. In walking or running the limb on the side of the spinal lesion begins to show features of rigidity. These changes, which will be discussed more fully in a subsequent communication and are adverted to in the appendix to this paper, are due, it seems probable, to the development of a scar in the spinal cord which spreads dorsally and involves long paths from higher centres [25, 26].

Myographic examination.—The method of experiment was to decerebrate at the intercollicular level under profound ether anæsthesia, to allow recovery, and after immobilizing all muscles except the two vasto-crurei either by nerve section or tendon resection, to investigate with an isometric myograph the effect upon a series of knee-jerks of a single inhibitory induction shock applied to the ipsilateral sciatic nerve. As was shown originally by Ballif, Fulton and Liddell [2] resistance to inhibition is rapidly re-established in a decerebrate preparation and only gradually after total spinal section. As a result of this myographic analysis it is found that even some months after the spinal lesion, the jerk on the unoperated side resists a single inhibitory ipsilateral break shock as markedly as a normal decerebrate preparation. Contrasted with this, the jerk on the side of the lesion is more susceptible to inhibition, and for a longer period. The effect is profoundest soon after operation, but gradually decreases with the passage of time, until, after about a year, it is slight and the recovery curves on the two sides are similar to the curves from preparations decerebrated without any preceding spinal lesion. Figs. 2 to 4 with their legends give the essential data of the experiments. The figures show the speed of recovery of the knee-jerks in three typical preparations. As a rule, in the first hundred days after the lesion there is greater susceptibility to inhibition on the one side. During the second hundred days recovery comes about. And in the third hundred days, heightened knee-jerks appear in the isometric records, while the regained resistance to inhibition continues, or even exceeds normal.

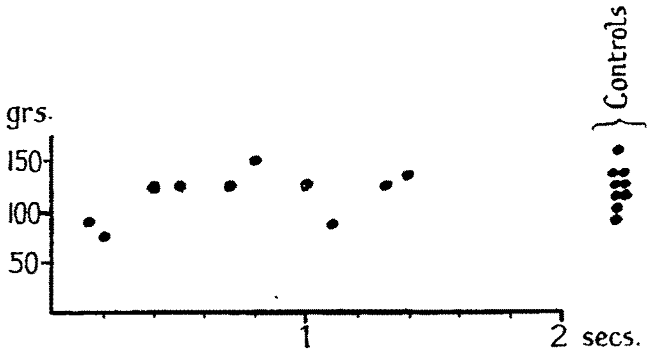


FIG. 2A.—Recovery curve of knee-jerk from inhibition on "normal" side, i e. without spinal lesion. Inhibition produced by single break-shock to ipsilateral sciatic nerve. Isometric myograph. Intercollicular decerebration. Ordinates, tension of jerk in grammes. Abscissæ, time after break-shock in seconds. Control jerks shown on the extreme right. Extension of muscle 3 6 mm. (total resting length 1,100 mm.), to develop initial tension for experiment of 75 grm. Tendon taps, 600 grm. given by index finger. Tendon movement × 60. The jerks were small because the preparation was so rigid that occlusion took place.

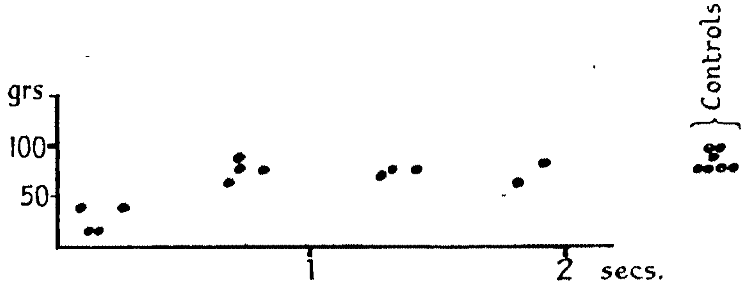


FIG. 2B.—Similar recovery curve from the same preparation on side of which a ventro-lateral lesion was made in the cord thirty-nine days previously. Extension of muscle 6 4 mm. to develop initial tension of 80 grm. Taps 500 grm. There is more inhibition in this limb as compared with opposite normal limb, fig. 2A. Extension of muscle was adjusted to give jerks comparable in tension to the normal jerks shown in fig. 2A.

Another item of evidence regarding the "spinality" of the limb on the side of the lesion is found by observing the degree of extension needed to produce adequate backgrounds of excitation.

Number of days since lesion	Resting length of muscle in cm.	Extension in mm. necessary to give adequate initial tension on myograph	
		Side of lesion	Opposite side
39	11·3	6·4	3·6
98	—	1·8	2·0
105	11·9	8·6	1·9
125	10·7	2·5	2·1
133	11·5	5·9	1·3
350	11·5	1·4	8·6
383	—	3·2	6·3

In the table are given figures from a selection of preparations. For the first 100 or 150 days, the knee extensor on the side of the lesion has to be lengthened more by lowering the table in order to give adequate initial tension. In other words, to give the same "tonic" pull at rest, that knee extensor's stretch-organs must themselves provide a greater measure of C.E.S. in the spinal centres owing to the diminution of background C.E.S. brought about by severance of the vestibulo-spinal tract on that side. After 300 days it is apparent that the position is

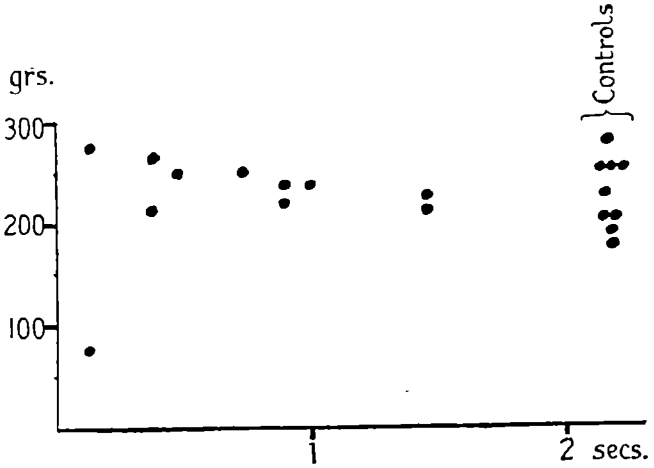


FIG. 3A.—Similar to fig. 2A, in preparation in which ventrolateral lesion was made in opposite side of cord 138 days previously. Extension of muscle 1·3 grm., to give initial tension of 90 grm. Length of muscle 1,150 mm. Taps 500 grm.

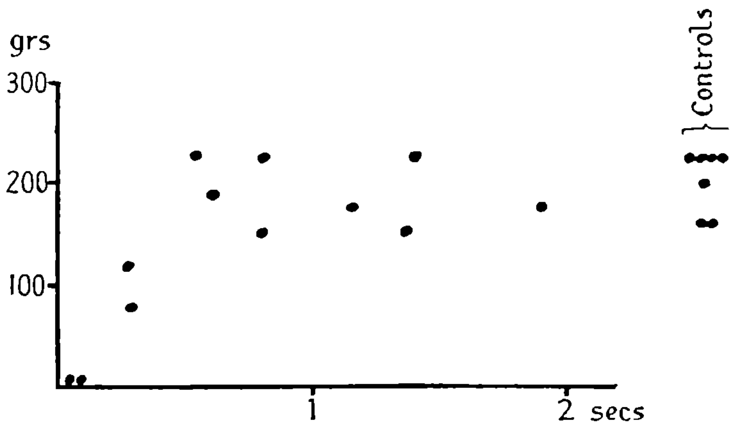


FIG. 3B.—Same preparation as fig. 3A, but on same side as the 138 days old lesion. There is greater inhibition on this side and the muscle needed 5·9 mm. extension to give initial tension of 115 grm. which was adequate for elicitation of a comparable jerk. Tendon taps 650 grm.

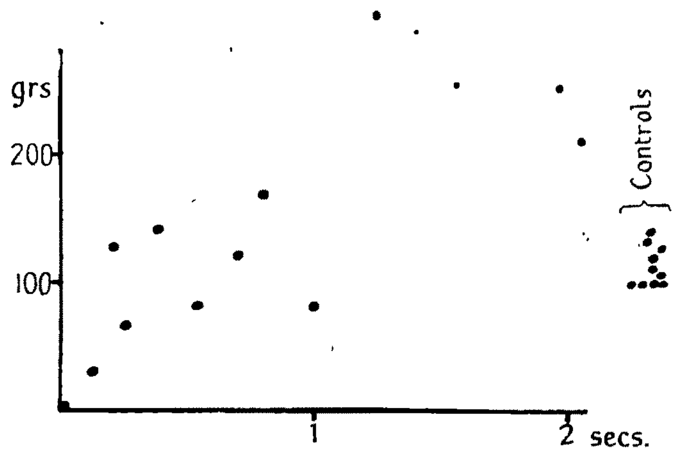


FIG. 4A.—Similar to figs. 2A and 3A, being the knee-jerk's inhibitory curve in preparation in which a ventrolateral lesion was made on opposite side of cord 350 days previously. Extension of muscle 3·6 mm. to give initial tension of 100 grm. Length of muscle 1,150 mm. Taps 175 grm. Although less resistant to inhibition than preparation in fig. 3A, the curve is within the limits of normality for a decerebrate preparation.

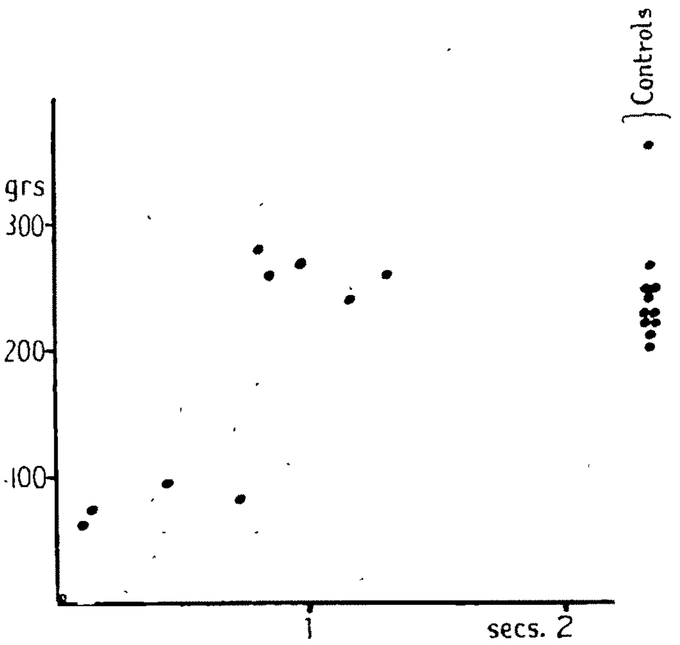


FIG. 4B.—Curve from side of lesion. The jerks are larger, although the extension of the muscle was less, 1·4 mm. Initial tension 50 grm. Taps 175 grm. "Overcompensation" has supervened as regards posture. Recovery curve from inhibition is similar to fig. 4A. In that respect also compensation established.

reversed and over-compensation, whatever its provenance or nature, has come into evidence. In the stage of over-compensation, the muscle on the side of the lesion needs less extension than the muscle on the "normal" side, in order to give the same initial tension, and that, be it noted (1), after ablation of all nervous structures headward of the inferior quadrigemina (2), in spite of, or because of, the spinal scar already mentioned. In all these preparations voluntary power had been excellent before decerebration. Histologically, the cord shows ipselateral degenerations in the ventro- and dorsolateral regions, but not in the dorsal columns.

In a number of preparations, spinal lesions were made laterally or dorsolaterally. Such preparations showed but little tendency to post-operative paraplegia or to distension and overflow of the bladder, presumably because the more accessible approach to the cord minimized operative trauma, slight though that was in the ventral approach. Ipsilateral limb rigidity [25] appeared on recovery from the operation, i.e. within two days, and it was of similar degree to that ensuing from the dorsally spreading scar after ventrolateral lesions, i.e. more than 1·0 kg. on the ipsilateral side, less than 0·5 kg. on the contralateral. When decerebrated at any time, the ensuing decerebrate rigidity was, as a rule, equal in the two hind limbs, or very slightly less on the ipsilateral side. There was no clear difference between the knee-jerks after decerebration, and increased inhibitability of the spinal centres was too slight to be detected, even if present. These findings, therefore, confirm the belief of Fulton, Liddell and Rioch, that, as concerns inhibitability of the knee-extensor's motor centres, the ventrolateral area of the cord is an area of special vulnerability, and lesions in it are followed by increased susceptibility to inhibition.

CONCLUSIONS.

(1) Lesions have been made in the ventrolateral area of the spinal cord of cats at the dorso-lumbar level. When the preparations are examined after intercollicular decerebration, there is found an increased susceptibility of the knee-jerk to ipsilateral inhibition.

(2) The susceptibility diminishes with time, and after the lapse of 100 days and before the lapse of 200 days, resistance to inhibition reaches normal value.

(3) The reflex resting tension of the knee-extensor also recovers gradually and approximately *pari passu* with increased resistance to inhibition.

(4) After 200 days there occurs over-compensation, both as regards inhibition and reflex resting tension.

(5) A sequel of ventrolateral lesions is a scar spreading dorsally (but not as far as the dorsal columns), whence arises a limb rigidity which is other than decerebrate rigidity and is itself abolished by intercollicular decerebration. The previously rigid limb then becomes flaccid. This flaccidity after decerebration is due to the original ventrolateral lesion.

I am indebted to the Christopher Welch Trust for a grant towards photographic expenses, to Mr. T. A. Marsland for microscopic preparations, to Mr. A. S. Chapman for his care in looking after the operated animals, and to Mr. C. Carr for his help with the experiments.

APPENDIX.

A NOTE ON THE "SPINAL" AND "DECEREBRATE" TYPE OF KNEE-JERK IN THE CAT.

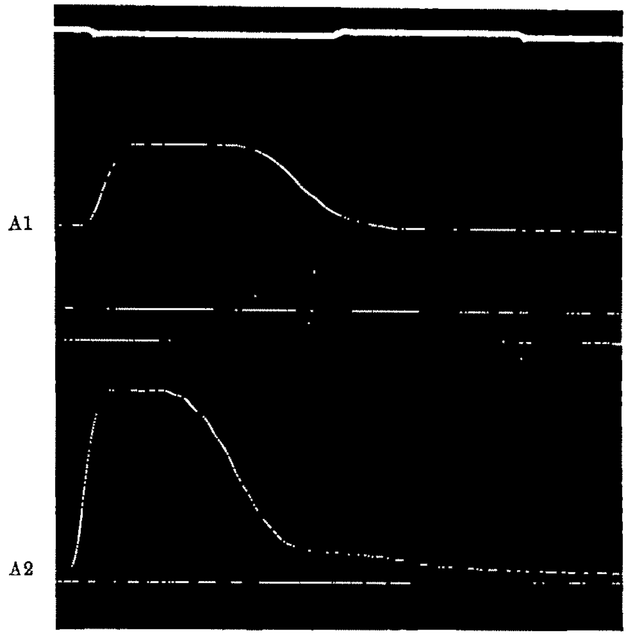
In the preceding paper it was mentioned that a sequel of lesions in the ventrolateral region of the cord is a scar which spreads dorsally (but not so as to involve dorsal columns), producing rigidity in the ipsilateral limb within two or three weeks, presumably by involvement of paths from high nerve centres [3, 25]. The rigidity lasted for a year or more (as long as the observations were made), and from the end of the first month to the fourth or fifth was very evident in the gait. It came into prominence especially when the animal was held up by the scruff of the neck and the two sides compared by manual and dynamometer pressure on the pads of the hind feet. The animals became friendly and docile, and when their attention was distracted by petting, the limbs could be examined without interference from voluntary movements. It was common to find, in a cat weighing 2 to 3 kg., that a dynamometer pressure of 1·0 kg. was needed to flex the rigid limb, whereas 0·1 kg. was sufficient for the normal limb [18]. When the rigid limb had once been flexed, its return to extension was so greatly accelerated by gentle pressure on the pad of the foot that the Magnet reaction [31] appeared to be in operation. At all times voluntary movement, when elicited, was good, so that serious impairment of cortico-spinal paths was improbable, though the rigidity in the one limb often hampered great activity or friskiness, and for walking, required circumduction of the limb. A "clasp-knife" effect was not detected, and resistance to passive flexion was maintained until flexion was complete. On occasion, the ipsilateral limb was so rigidly extended that its knee-jerk was occluded. In the experiments now to be described, the animals were decerebrated at intercollicular level, so that long paths beginning (or ending) above that level were severed. The severance of the vestibulo-spinal tract of the cord achieved by the original lesion in the ventrolateral area remained with the same pattern of effect as before, though now no longer a palimpsest with higher nerve patterns.

When such a preparation is examined after decerebration, it is found that on the unoperated "normal" side the limb shows all the well-known plastic characteristics, such as shortening and lengthening reactions and "clasp-knife" rigidity [24, 4]. But on the side of the lesion there is marked alteration. The limb on that side is now flaccid. Removal of nerve-tissues headward of the intercollicular level has, in fact, banished rigidity in that limb, and reveals the preparation in the familiar aspect of a decerebrate preparation which has suffered unilateral loss of the vestibulo-spinal tract. That decerebration at intercollicular level should abolish the previous rigidity shows, in brief, that it and decerebrate rigidity have neither a common provenance nor closely related source, but impress a somewhat similar pattern of effect on the lower reflex arc. Such a conclusion is more than anticipated by Sherrington's account of decerebrate rigidity when he found that unilateral extirpation of a cerebral hemisphere produced ipsilateral rigidity, but stimulation of the motor area in the remaining opposite hemisphere inhibited the rigidity [27]. Without gaining for the present much further insight into the origin of the rigidity previous to decerebration, it is appropriate to recall Hughlings Jackson's dictum on the rigidity of hemiplegia that negative states of nervous centres cannot cause positive states, though they may permit them. The established belief in the inhibitory action of the cerebral hemispheres on extensor tone and its appearance after cerebral lesions has received much experimental support [5, 14, 15, 16, 17, 22, 24, 30]. But removal by decerebration of such limb rigidity has not often been described in the literature. This problem will be discussed more fully in a later paper [20].

The clinical changes brought about by decerebration can also be effected qualitatively by moderate anæsthesia from nembutal (35 mgm./kg. *i.p.*) Nembutal, indeed, appears to produce in that respect a sort of pharmacological decerebration. The properties of dial are very similar [13]. During nembutal anæsthesia there is not, it is true, any great degree of decerebrate rigidity in the normal leg, but there is in it much more postural tonus (which is the same thing) than in the leg on the side of the spinal lesion, which is completely flaccid. The knee-jerks have the same qualitative characters as after surgical decerebration. Since the administration of nembutal has the advantage over surgical decerebration that recovery to the cerebrate state ensues in a few hours, periodical examinations under nembutal became customary, and the progress of the animal's condition was followed by its aid. At the close of the period of observation, that is after a period of from one to fifteen months, surgical decerebration brought confirmation of the reactions under nembutal. At the same time, it was demonstrated on every occasion that the difference between the jerks on the two sides was not due to any action of the flexor muscles, since the differences were not affected by paralysis of the flexors by nerve section.

EXAMINATION OF THE KNEE-JERK.

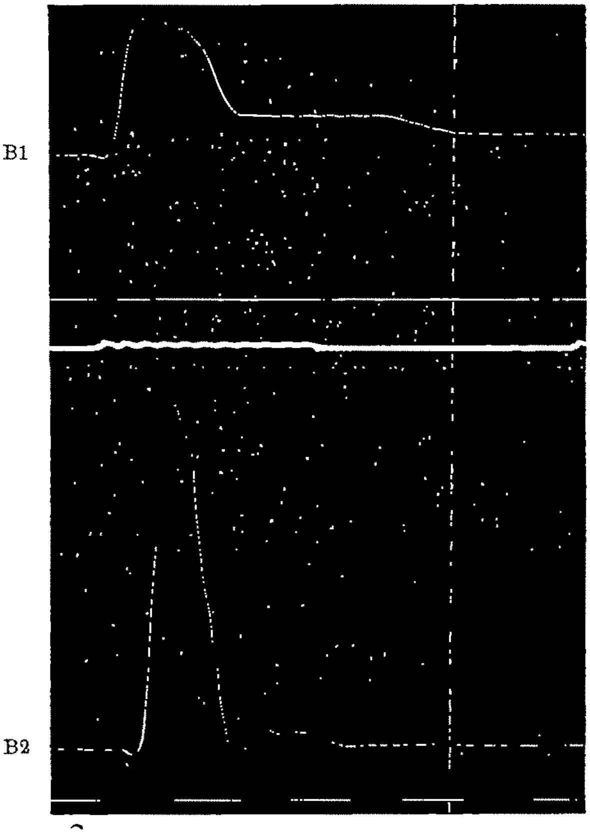
When a preparation in which a ventrolateral lesion in the spinal cord has been made previously is examined in the supine position: (*a*) Under moderate anæsthesia by nembutal; or (*b*) after surgical decerebration at intercollicular level, it is found that the knee-jerks are very different on the two sides. To elicit the jerk, a percussion hammer is used, of the National Hospital pattern, though with a rigid and not a whalebone handle. Such a hammer is, therefore, relative to the cat a large hammer, engaging, probably, all or most of the stretch-receptors in cat's muscle. In order to obtain graphic records a recording mechanism was employed which consisted of a bell-crank lever with a myograph arm of straw and a frontal writing point of parchment, writing upon a smoked drum. The animal was laid supine, in a rigid cradle, with the thighs supported by a padded bar and the legs dependent. The animal's foot was encased in a light shoe which was attached by a thread to the vertical arm of the myograph. The lever of the myograph was restrained by an elastic band, so that the mechanism was neither strictly isotonic nor isometric. Tendon movement was magnified four times. Isometric examination, although it has yielded a wealth of information, is not conformable with most voluntary muscular contractions (except in "tug-of-war") because it does not permit of shortening. Isotonic myographic examination, on the other hand, although conformably similar to most muscular activities has been a fertile source of



A.—Records of knee-jerks made with myograph which was mainly isotonic and allowed shortening, but was also isometric, through the restraint of a rubber band. Frontal writing point. Tendon movement multiplied four times. Top, A1, knee-jerk on normal side, preparation under nembutal. Bottom, A2, jerk on side of ventrolateral spinal lesion made 33 days previously. Difference in initial tension less than 10 grm. Time 0·6 secs.

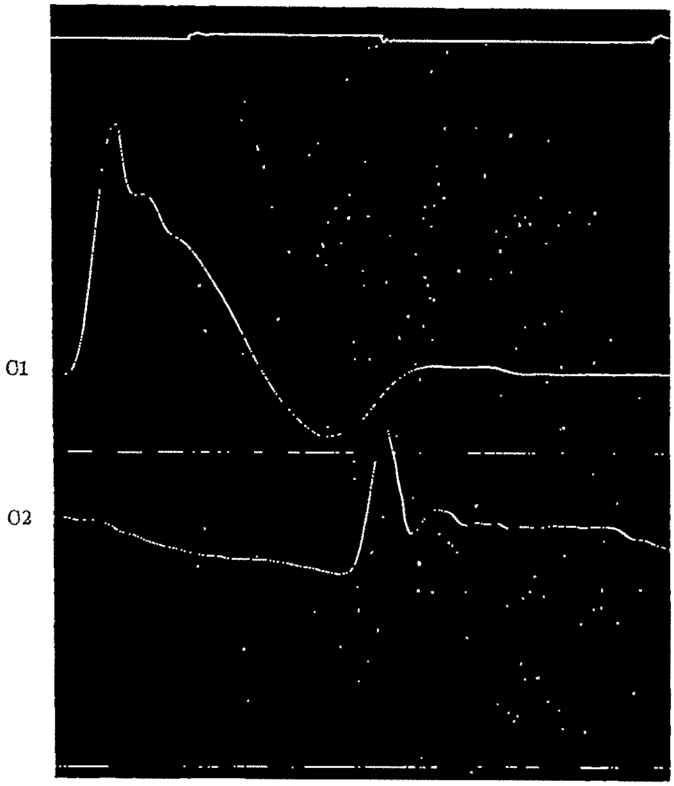
erroneous conclusions in which the mechanical properties of levers have been interpreted as physiological phenomena. But since it is an isotonic contraction which is observed in clinical examination of the knee-jerk, myographic recording which is mainly isotonic and only isometric to the degree of reducing instrumental error, seems to be the logical method.

At myographic examination, confirming previous clinical examination, the knee-jerk on the side of the spinal lesion, especially in the first hundred days, rises freely and abruptly, and then falls abruptly (figs. A2, B2), the limb oscillating two or three times after reaching the base-line (fig. B2). The oscillations are not so clear in the myograph records as in the free state of the limbs. On the normal side, however, the rise of the jerk is more gradual, its turn at the summit is more gradual as a rule, and its return to the base is gradual and not



B.—Same preparation, five days later and three hours after decerebration at intercollicular level. Difference in character is maintained and accentuated. There is less posture on the side of the lesion (bottom record) and so much "fling" that the writing point fails to trace the upper part of the rapid upstroke. This preparation also provided the recovery curves of fig. 2 (isometric records) in preceding paper.

followed by oscillations (figs. A1, B1). The difference between the jerks is reminiscent of the difference between a freely vibrating spring and a damped spring. Of the threshold value of the stimulus, it can be said that in the free or isotonic state adequate stimulation of the ipsilateral knee is apparently achieved by a lighter tendon tap, e.g., from a pencil, than is the contralateral (normal) knee. Under those conditions, however, the slight tap to the normal knee may be held to elicit such a small response that it is occluded by the strong postural background. Under strict isometric conditions, on the other hand, in the first seven months after the spinal lesion, a higher threshold is known to exist on the ipsilateral side, that is to say, a higher static initial tension must be applied to the tendon to produce an adequate background of C.E.S., and often, in addition, higher kinetic tension in the tap (figs. 1 to 4). The disparity, there-



C.—Similar to B, 138 days after lesion in ventrolateral region and two and a half hours after decerebration at intercollicular level. Top record, C1, from side of lesion. Bottom record, C2, from normal side. Difference between initial tension of two records is 10 grm. The normal jerk is more peaked than usual, but at every level it is broader than on the operated side. These records show also that, in spite of partial occlusion of the jerk on the normal side . (i) the jerk on that side has greater breadth, (ii) the difference is evident as late as 138 days after the lesion, though much diminished. Posture has appeared on the operated side (top record).

fore, between the necessary tensions under isotonic and isometric conditions is more apparent than real.

The most noticeable feature in the isotonic record is the sharp steep rise of the jerk and its height, on the side of the lesion (fig. B2). In that phase of movement, inertia of the lever could not account for the steepness of the rise, but would rather tend to reduce it. Nearer the summit the inertia of the lever will induce errors, even though the lever is partly isometric in virtue of the rubber band, and in the present series that segment of the record does not merit too close analysis, though its general contrast with the restrained sweep of the normal knee-jerk is significant of the difference existing between the two sides. As a rule, the plateau of the jerk on the normal side (fig. B1) is longer than on the operated side. It is never shorter. Its length must be ascribed to "tonic after-discharge," since the other factor which could produce a longer plateau, that is increased initial tension, though here too slight, being only a few grammes (less than 10) might, if more considerable, and under more strictly isometric conditions, operate in favour of the other leg which is known, from isometric records, to need greater initial tension (see p. 164).

These differences are most marked in the first hundred days after the spinal lesion. Thereafter they diminish, but are easily demonstrated during or after the second hundred days, when there is some posture on the operated side (fig. C1 and C2).

DISCUSSION.

Taking these features as a whole, one sees on the normal side how "posture follows movement like a shadow." On the operated side graduality of movement is lost by the absence of posture.

One feature of the jerk on the operated side cannot so readily be ascribed to the absence of posture. That feature is the rapid rise. Posture, if present-day beliefs are correct, maintains or tends to maintain an already existing tension in the muscle's tendon, but does not markedly affect the speed of contraction, though a small increase is theoretically possible as a result of sub-threshold fringe effect [4]. But in the operated limb there is an absence of posture, and that is the limb with the rapidly-rising jerk. Some other line of argument must therefore be sought. There may, for instance, be a more synchronous central discharge from the reflex centres when posture is absent, though it has not been observed by workers with electrical methods. But it occurs in flexor muscles, and there is ample evidence, myographic and electrical, of release after spinal transection [7, 28, 21]. For extensors, however, after spinal transection, the quicker white muscle is inactivated from shock, leaving only slow red muscle [6]. Alternatively, extensor's central discharge may have been slowed [23]. Now isotonic contractions of muscles, as is well-known, can be slowed by fatigue, and there ensues an increased height in the isotonic myogram, as in the staircase phenomenon. In the present series of experiments sections of certain spinal tracts has been made, so that in many of its reactions the muscle's behaviour is "spinal" in type.

Slowness of contraction, whatever its cause [2, 6, 23], is a feature of " spinal " behaviour. Hence the slow " spinal " muscle may endow the myograph lever with greater inertia so that it reaches a higher level. This explanation, however, is somewhat weakened by the fact that the lever is not purely isotonic and that its inertia is checked by the indiarubber band, which, when the lever is unattached, brings it rapidly to the base line. Another possibility is favoured when slow muscle is active. It has been noted by Fröhlich [8] and quoted thus by Adrian [1] : " increased duration of the contraction may lead to an actual increase in the tension exerted by the whole muscle, because the longer the duration the more chance there is that all parts of the muscle will be fully contracted at the same moment." This seems a very probable explanation of the higher contraction of the spinal knee-jerk.

Yet another possibility, however, deserves mention. In a tonic muscle, since some stretch-receptors appreciate tendon-tension and are active, so that some muscle fibres, as effectors in the reflex arc, are contracted, there is, thanks to the parallelism of fibres, protection of other tension-receptors from the tendon's pull, and they remain inactive. Hence when the tendon is tapped, these other tension-receptors are thrown into activity *seriatim*, that is, they are recruited, with the result that the reflex response of the tonic muscle is a gradual rise. The state of affairs in the atonic muscle is, however, far different. In such a muscle, if the stretch-receptors are active (and there is no reason to suppose that they are not), their excitation falls upon the group of central motoneurones in a state, as they are in these experiments, of partial though severe, spinal shock, i.e. with diminished low grade C.E.S., so that the motor centre remains unresponsive to scattered stimuli from the muscle. In consequence, the muscle is slack. In such a muscle, therefore, few or no stretch units are protected by the pre-existing activity of other muscle groups as they are in the tonic muscle, and all stretch units are equally susceptible to a tendon-tap, which, when it comes, throws all or nearly all stretch units into activity almost synchronously, and an almost synchronous volley of impulses travels to the reflex centre. The consequent reflex discharge is almost synchronous, or at least more synchronous than in the tonic leg, and an abruptly rising knee-jerk is the outcome. Hence may ensue the steep rise and fall in the almost apostural jerk, and the gently graduated (recruited) rise and fall in a more actively tonic muscle. Which of these arguments, favouring the theory of slow muscle or the theory of peripheral recruitment of stretch units, should be invoked in whole or in part, must remain an open question until electrical records have been made. Two other and subsidiary conditions which might affect the field of experiment deserve to be mentioned: (*a*) In postural muscles, occlusion tends to reduce the size of the tendon-jerk, but under the conditions of these experiments, differences in resting tension—only a few grammes—are too slight to produce substantial difference between the two sides. (*b*) These experiments were performed when some measure of recovery from spinal shock had come about. If a completely atonic muscle had been examined, there would, of course, have been no jerk because C.E.S. would be always of sub-threshold value.

Finally, there deserves to be mentioned autogenetic inhibition of muscle [4] which, if it is a reality in spite of some recent evidence to the contrary, may well suffer abeyance by severance of long ascending spinal paths, so that the "spinal" muscle is free to give a rapidly and high rising jerk, whereas the "decerebrate" muscle is not.

SUMMARY.

The mechanical differences between spinal and decerebrate knee-jerks have been examined with a rubber-checked isotonic myograph, and probable causes for these differences are discussed and analysed. Thus, any slow muscle gives an increased height of response with an isotonic lever, and "spinal" muscles are slow muscles. Also, in any apostural muscle it is probable that a tendon-tap promotes greater synchronicity of discharge than in a postural muscle, where recruitment of stretch organs is inevitable. Both these factors may contribute to the larger excursion of the "spinal" jerk.

With the passage of time, the differences become less sharply defined, but are detectable in all preparations for at least 200 days.

REFERENCES.

[1] Adrian, E. D. *Journ. Physiol.*, 1920, **54**, 1.

[2] Ballif, L., Fulton, J. F., and Liddell, E. G. T. *Proc. Roy. Soc.*, 1925, **98B**, 589.

[3] Cairns, H., and Fulton, J. F. *Lancet*, 1930, **ii**, 16.

[4] Creed, R. S., Denny-Brown, D. E., Eccles, J. C., Liddell, E. G. T., and Sherrington, C. S. "Reflex Activity of the Spinal Cord," 1932.

[5] Cooper, S., and Denny-Brown, D. E. *Proc. Roy. Soc.*, 1927, **102B**, 222.

[6] Denny-Brown, D. E. *Ibid.*, 1928, **104B**, 251.

[7] Forbes, A., Cobb, S., and Cattell, H. *Amer. Journ. Physiol.*, 1923, **65**, 30.

[8] Frohlich, F. W. *Z. Allg. Physiol.*, 1905, 5, 288.

[9] Fulton, J. F., Liddell, E. G. T., and Rioch, D. McK. *Journ. Physiol.*, 1930, **69**, xxvii.

[10] *Idem.* *Ibid.*, 1930, **70**, xxii.

[11] *Idem.* *Brain*, 1930, 53, 311.

[12] *Idem.* *Ibid.*, 1930, **53**, 327.

[13] *Idem.* *Journ. Pharm. Exper. Therap.*, 1930, **40**, 423.

[14] Fulton, J. F., and Keller, A. D. "The Sign of Babinski," 1932.

[15] King, W. T. *Amer. Journ. Physiol.*, 1927, **80**, 311.

[16] Langworthy, O. R. *Johns Hopkins Hosp. Bull.*, 1928, **42**, 20.

[17] Laughton, N. B. *Amer. Journ. Physiol.*, 1928, **85**, 78.

[18] Liddell, E. G. T. *Journ. Physiol.*, 1934, **82**, 20.

[19] *Idem.* *Brain*, 1934, **57**, 386.

[20] *Idem.* In preparation.

[21] Liddell, E. G. T., Matthes, K., Oldberg, E., and Ruch, T. C. *Brain*, 1932, **55**, 239.

[22] McKibben, P. S. *Anat. Rec.*, 1929, **42**, 57.

[23] Martin, P. *Compt. Rend. Soc. d. Biol.*, 1931, **106**, 1257.

[24] Olmsted, J. M. D., and Logan, H. P. *Amer. Journ. Physiol.*, 1925, **73**, 570.

[25] Ranson, S. W., and Zeiss, J. C. and F. R. *Journ. Comp. Neurol.*, 1932, **54**, 13.

[26] Ranson, S. W. *Ibid.*, 1932, **55**, 91.

[27] Sherrington, C. S. *Journ. Physiol.*, 1897, **22**, 319.

[28] Sherrington, C. S., and Sowton, S. C. M. *Ibid.*, 1915, **49**, 331.

[29] Spiegel, E. A. "Der Tonus der Skelettmuskulatur," 1927.

[30] Warner, W. P., and Olmsted, J. M. D. *Brain*, 1923, **46**, 189.

[31] Magnus, R. *Lancet*, 1926, **ii**, 531, 585.

THE ORIGIN OF THE POSTERIOR CEREBRAL ARTERY.[1]

BY D. J. WILLIAMS (MANCHESTER).

ABBIE [3] has recently described the comparative anatomy of the posterior cerebral and posterior communicating arteries. He has agreed with Shellshear, Stopford and others, who have affirmed from anatomical evidence that the posterior cerebral artery, although functionally a branch of the basilar artery, is morphologically one of the terminal branches of the internal carotid artery.

This paper advances evidence on this subject derived from a study of the perivascular innervation of the cerebral vessels.

METHOD.

Normal adult human brains were used. The great vessels comprising the Circle of Willis and its main branches were carefully dissected from the brain tissue, the adventitia and the perivascular structures being maintained as intact as possible. The vessels having been fixed in formol saline, were stained by Stöhr's modification of Schultz's silver impregnation method [6]. Stöhr's technique was still further modified. It was found that the original method caused extremely rapid precipitation of silver on the surface of the tissues; reduction was complete in a few seconds, and therefore could not be efficiently controlled. When the stock solution of hydroquinone was used in a solution of 1 : 180, optimum reduction occurred in about eight to ten minutes. After mounting the tissue it was found that reduction continued to occur slowly and caused staining of the mounting medium by diffusion. To obviate this the tissues were fixed in five per cent. sodium hyposulphite for seven to ten minutes, and were afterwards well washed in tap water. The specimens were then mounted in glycerine and were examined under a dissecting microscope. The perivascular nerve network was stained uniformly black, while the connective tissue of the tunica adventitia remained a golden brown shade.

RESULTS.

The plexuses on the vertebral arteries were readily distinguished by means of the dissecting microscope and they were followed cranially.

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[1] Work carried out in the Departments of Anatomy and Surgery in the University of Manchester, during tenure of the Professor Tom Jones Memorial Fellowship in Surgery.

The sympathetic nerve fibres were traced with ease on to the basilar artery in four adult human brains. The plexus on this artery was simple in type and was less dense than that on the internal carotid artery, which formed an intricate network around the vessel. The vertebral plexus extended on to all the symmetrical branches of the basilar artery. In many instances solitary non-myelinated nerve fibres were traced on to the small pontine branches of the basilar artery. They could not, however, be followed into the substance of the pons.

At the upper extremity of the basilar artery, at the point of origin of the two posterior cerebral arteries, the perivascular innervation was scanty and of a very simple plexiform structure. The plexus divided and extended on to the adventitia of the vessels. The nerve fibres extended as far as the junction of the posterior communicating artery with the posterior cerebral artery. In no case did it extend along the posterior cerebral artery, nor did it continue on to the posterior communicating artery. Although the vertebral plexus ceased at this level, both of these arteries were liberally supplied with a perivascular nerve network (figs. 1 to 3).

The internal carotid plexus was then traced on to the middle cerebral artery. This plexus was, as has been stated, very dense. The nerve fibres extended along the middle cerebral artery, and could be seen on the tunica adventitia of its larger branches. They pursued a more simple and discrete course along these vessels than on the parent trunk. At the point of origin of the posterior communicating artery a very large division of the perivascular nerve fibres occurred. The plexus ran along the posterior communicating artery in the form of parallel bundles. The number of nerve fibres was greatly in excess of the usual perivascular innervation of so small a vessel. At the junction of the posterior communicating artery with the posterior cerebral artery this caudal flow of the carotid plexus swept on to the latter artery, and was continued along the artery until its terminal branches were reached (figs. 1 to 3).

In five of the eight specimens examined there was no apparent communication between the terminal nerve fibres of the vertebral plexus and the posterior flow of the carotid plexus. In three cases one fine twig appeared to join a nerve fibre from the posterior communicating artery (fig. 3). No other connection could be demonstrated between the two perivascular systems. Structurally they were quite discrete. The vertebral perivascular nerve plexus extended on to the basilar artery and on to all of its larger branches, including the commencement

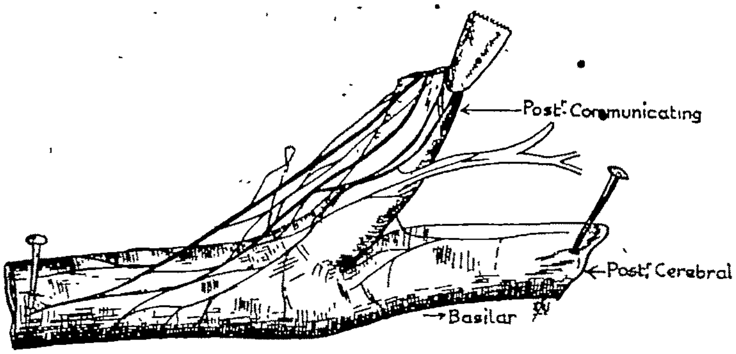

FIG. 1.

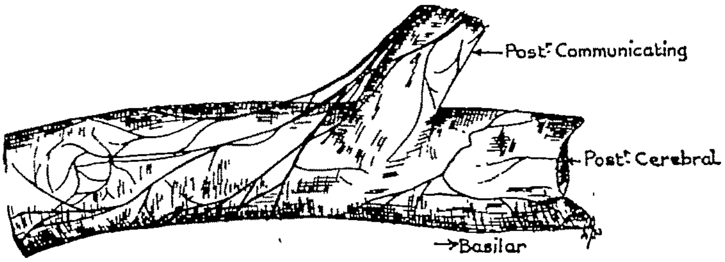

FIG. 2.

FIGS. 1 and 2.—Drawings of the junction of the posterior communicating artery with the posterior cerebral artery, stained to show the perivascular nerve network. Comparatively large nerve bundles are seen running from the posterior communicating artery on to the distal portion of the posterior cerebral artery. There they divide to form a typical perivascular plexus. Fine nerve fibres on the proximal part of the artery, derived from the vertebral plexus, have no connection with the carotid fibres.

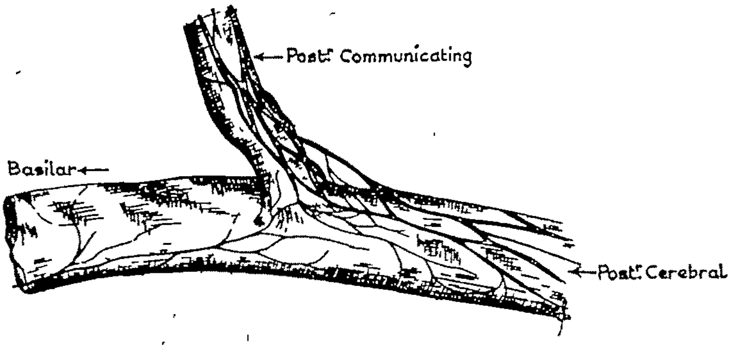

FIG. 3.—A similar specimen to those seen in figs. 1 and 2. Here a minute bundle of the vertebral nerve fibres is seen joining a bundle from the carotid system.

of the posterior cerebral artery. The carotid plexus innervated the anterior and middle cerebral arteries, and the posterior also, via the small posterior communicating artery.

Discussion.

This innervation of the posterior cerebral artery from the perivascular sympathetic plexus of the internal carotid artery is of phylogenetic interest. Abbie [2 and 3] recently described the comparative anatomy of the posterior cerebral artery. Briefly he showed that in amphibia (Rana) this artery was developed from the hippocampal artery of the lower forms. In reptiles (Sphenodon) it was mainly the hippocampal artery which had acquired a nearer source of origin for its blood, by means of a more posterior anastomosis with the cranial division of the internal carotid artery. In mammalia (Sheep) he found that the posterior communicating artery was larger than the posterior cerebral artery. In sub-primates the posterior communicating artery ran from the internal carotid artery to the basilar artery, and it was clearly the caudal division of the internal carotid artery. In primates the change is complete, and in man, except where developmental anomalies occur, the posterior cerebral arteries are apparently the terminal branches of the basilar artery.

Many observers have described wide variations in the anatomy of the posterior communicating artery. Stopford [7] found that it was greater than the posterior cerebral artery on both sides in 2 per cent. of cases and on either side in 4 per cent. of a series of cases that he examined. He described a case where, in the absence of a posterior communicating artery, the posterior cerebral artery arose as a continuation of the internal carotid artery, no anastomosis with the basilar artery being present. Fawcett and Blachford [4] found absence of the posterior communicating artery in 1·8 per cent. on the right, and in 1·4 per cent. on the left side. In these cases the posterior cerebral artery sprang directly from the internal carotid artery. Abbie [1] has described wide variations in the anastomosis between the anterior choroid, posterior communicating and posterior cerebral arteries.

During the present investigation the cerebral arterial tree of four early fœtuses was examined. In all the posterior communicating artery was relatively larger and thicker than in the adult, and its lumen was relatively wider. In one specimen, aged 9-10 weeks (fig. 4), it was equal in diameter to the posterior cerebral artery on one side, and greater than it on the other. Stopford [7] has stated that the importance of the posterior communicating artery is much greater in intrauterine life, when it represents the origin of the posterior cerebral artery from the internal carotid artery. The perivascular innervation of the posterior cerebral artery which has been described in this paper is a striking confirmation of the views expressed by these previous workers. It is axiomatic that the nerve supply of any tissue follows that tissue from its ontogenetic point of origin. The posterior cerebral artery, deriving its whole innervation from the internal carotid system via the posterior communicating artery, would therefore appear to be morphologically a branch of the internal carotid artery. That is, all the cerebral arteries, anterior, middle and posterior, are fundamentally a complete system. Therefore that portion of the posterior cerebral artery between the basilar artery and the posterior communicating artery, and not the posterior communicating artery itself, is the true connecting link between the vertebral and carotid vascular systems.

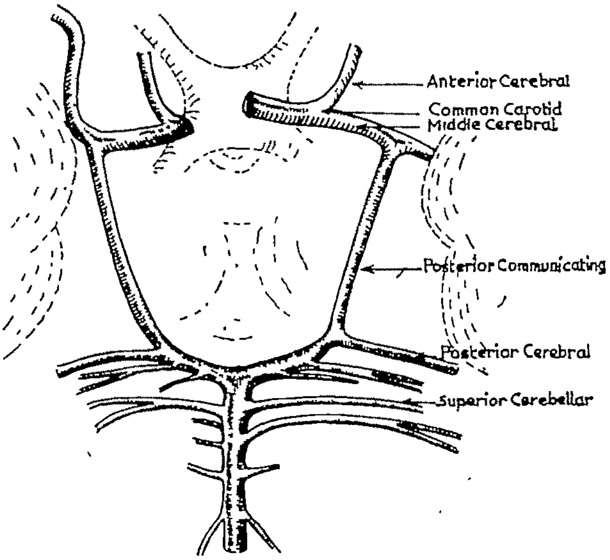

FIG. 4.—The Circle of Willis of a ten weeks' fœtus. The posterior communicating arteries compared with those of the adult, are much thicker and longer. In this specimen they are as wide as the anterior and middle cerebral arteries.

Shellshear [5] has postulated that the distribution of arteries obeys some definite ontogenic and phylogenetic law. He has stated that the evolution of the vessels is dependent on, and proceeds hand in hand with, the evolution of their fields of distribution. Thus, as Abbie has said, the arteries of the brain, being as much a part of the neurovascular mechanism as the brain itself, have shown changes concurrent with the more specialized development of the central nervous system. As the brain has expanded to meet new and increasing requirements, its arteries have extended to satisfy the increased functional demands. In the backward growth of the cerebral hemispheres over the mid-brain the distribution of the posterior cerebral arteries has been separated further and further from the parent trunk, the internal carotid artery. In accordance with natural economy a nearer course of supply has been found in the anastomosis of the basilar artery with the posterior cerebral artery. Concomitant with the increasing functional demands of the posterior cerebral artery, the basilar artery has enlarged adequately to supply the increasing amount of cerebral tissue. Although functionally the posterior cerebral artery is a terminal branch of the basilar artery, morphologically it is one of the three terminal branches of the internal carotid artery. The carotid system is therefore distributed to the whole of the fore- and mid-brains while the phylogenetically older vertebral system is strictly confined to the hind-brain.

SUMMARY.

In man, the development of the cerebral cortex has been such that the original distribution of the vessels can only be ascertained indirectly; first, by comparison with lower forms; secondly, by the variations from the normal picture; thirdly, by the condition in the early fœtus; and lastly, by a study of the perivascular nervous network.

In this paper the perivascular innervation of the posterior cerebral artery has been shown to be derived from the carotid sympathetic plexus. The condition of the vessels in the fœtus has been described and previous work on their morphology has been summarized.

All the evidence produced confirms the view that the posterior cerebral artery is morphologically a terminal branch of the internal carotid artery.

BIBLIOGRAPHY.

[1] ABBIE, A. A. "The Clinical Significance of the Anterior Choroidal Artery," *Brain*, 1933, 56, 233.

2] *Idem.* "The Blood Supply of the Lateral Geniculate Body," *Journ. Anat.*, 1933, 67, 491.

[3] *Idem.* "The Morphology of the Forebrain Arteries," *Ibid.*, 1934, 68, 433.

[4] FAWCETT, E., and BLACHFORD, J. V. "The Circle of Willis. An examination of 700 specimens," *Journ. Anat. and Physiol.*, 1906, 40, 63.

[5] SHELLSHEAR, J. L. "The Basal Arteries of the Forebrain," *Journ. Anat.*, 1920, 58, 27.

[6] STOHR, PHILIP. In "Handbuch der Micr. Anat. des Menschen." W. Mollendorf. Berlin, 1928, iv, part 1, 1935.

[7] STOPFORD, J. S. B. "The Arteries of the Pons and Medulla," *Journ. Anat*, 1915, 50, 131.

MENINGITIS SEROSA CIRCUMSCRIPTA SPINALIS (SPINAL ARACHNOIDITIS).

BY J. ST. C. ELKINGTON.

In 1903, Spiller, Musser, and Martin [1] reported in some detail a case of spinal compression which was operated upon for a suspected spinal tumour and in which laminectomy revealed only a localized collection of fluid, under great tension, in the pia-arachnoid. No cause for this unusual accumulation of fluid was discovered. The patient recovered completely.

From this time similar cases are to be found in the literature, and in 1908 we find one reported by Mendel and Adler [3] under the title of "Meningitis Serosa Spinalis."

In discussing, in a subsequent paper, the nature of idiopathic collections of fluid in the subarachnoid space, Spiller [5] stated that practically nothing was known of their ætiology, and it was not until 1909 that the first attempt to define and describe this clinical entity was made by Sir Victor Horsley [6] under the title of "Chronic Spinal Meningitis."

He reported two cases in detail, and stated that he had operated on twenty-one in all. He regarded the condition as more common than spinal tumour, for which it was usually mistaken before operation. The essential change was a localized collection in the spinal subarachnoid space of fluid under great pressure, with secondary changes in the spinal cord which was often shrunken and on microscopy showed "meningogliosis." All Horsley's cases occurred in adults and he was inclined to attribute them to syphilis and gonorrhœa, stating his opinion that trauma played no part in their causation.

In spite of Horsley's paper the ætiology and clinical features of the condition remained obscure, and in 1910 Munro [9], in describing a number of cases, wrote "there is a something that produces a grave paralysis which is demonstrated clinically which appears totally inadequate and for which we have no corresponding experimental or post-mortem explanation."

From this time more numerous contributions to the subject appear in the literature under various titles, namely "Meningitis Circumscripta Spinalis," "Meningitis Serosa Spinalis," and "Chronic Spinal Arachnoiditis," and they fall naturally into two groups.

The majority of papers are simple case records with little or no further comment. Of these may be mentioned those of Bruns [2], Mendel and Adler [3], Bliss [4], Mills [7], Weisenburg and Müller [8], Kennedy [10], Bouché [11], Skoog [12], Batten [13], Marburg [14], Bausamer [16], Moniz [17], Barré [18], Grinker [19], Hiller [20], Kron [21], Hassin and Andrews [23], Guillain [25].

The minority of contributions present a series of cases with details of pathological investigations, operative findings and in some cases post-mortem material, and attempt to define the clinical features and ætiology of the condition. Of these the most noteworthy are the papers of Stookey [22], Mauss and Krüger [15], Vincent [24], Paulian and Turnesco [29].

Post-mortem material is unfortunately scanty, and detailed descriptions of the pathological findings are confined to the papers of Grinker and Marinesco. These contributions will be further referred to in separate sections of the following.

The present paper consists of an analysis of the symptoms and signs observed in forty-one cases of meningitis serosa circumscripta spinalis.

Only three of these were under the direct observation of the writer. The remainder were all under the care of past or present members of the staff of the National Hospital, Queen Square, and to them the writer expresses his gratitude for their permission to make use of the case notes. He is particularly indebted to Dr. Gordon Holmes for his unfailing advice and interest in the preparation of the paper and to Dr. J. G. Greenfield for his assistance in examining the pathological material and for the records of cerebrospinal fluid examinations.

In all cases there was reasonable confirmation of the diagnosis by laminectomy and in some cases by autopsy. With four exceptions the operations were performed by the late Sir Percy Sargent, and his private notes have been available for study and provide a valuable description of the operative findings. Owing to their length and number it is impossible to publish the clinical protocols of the cases.

Although in the recent literature on the subject the term "chronic spinal arachnoiditis" is more often employed, in the present contribution the title, "Meningitis Serosa Circumscripta Spinalis," will be retained as it does not suggest a limitation of the pathological process exclusively to the arachnoid.

Ætiology.—Analysis of the cases throws some light upon the distribution and ætiology of the condition. The disorder is distinctly commoner in men than in women. Of forty-one cases, thirty occurred in males and eleven in females. It might be supposed that this preponderance of male cases was due to the greater frequency of trauma and venereal infection in this sex, but in the group of cases in which no predisposing factor could be traced (eighteen) the same disproportion was observed, i.e. there were thirteen male and five female cases.

Although Hiller has reported a case occurring in a boy of 8 years, writers are agreed that the disease is predominantly one of middle life. This is confirmed by the present series in which the youngest case came under observation at 23, the oldest at 65; the average age of the patients when first seen was 45·1 years. Arranged in age-periods the forty-one cases are grouped as follows:—

Under 20 years	0 cases
20 to 30 ,, ...	6 ,,
30 ,, 40 ,, ...	6 ,,
40 ,, 50 ,, ...	14 ,,
50 ,, 60 ,, ...	10 ,,
60 ,, 70 ,, ...	5 ,,

Many different views have been put forward as to the cause of meningitis serosa circumscripta. Horsley suggested that syphilis and gonorrhœa were responsible and that trauma played no part, while Mauss and Krüger report in detail fifty-four cases following war injuries in which the traumatic origin appears indisputable. Others have regarded it as the consequence of various systemic infections, and Bouché specifically mentions typhoid. An association with spinal tuberculosis and arthritis of the spine is mentioned by Vincent. Several cases have been recorded following meningococcal meningitis (Batten, Holbaum, Guillain). The case reported by Kron followed a septic abortion.

Analysis of the present material amply confirms the inference that there are various conditions capable of initiating a similar process in the spinal meninges, and that there is, in fact, no single cause of the disease.

Of forty-one cases it was impossible in eighteen to trace any previous illness or injury which might have been the cause of the spinal condition. In many of these the usual illnesses of childhood were recorded; in one glycosuria was present; and in two a carbuncle had occurred some years previously.

In the remaining twenty-three cases, however, one or more possible causal factors were present, as follows:—

Trauma.—In nine cases a history of spinal trauma was obtained.

The interval between the injury and the onset of cord symptoms varied widely, being as short as three weeks in one case and as long as twenty-four years in another. The severity of the injury was equally inconstant.

Case 16 fell some distance on to her feet, and although the only symptom at the time was vomiting, radiograms taken eighteen months later showed a compression fracture of the 3rd and 4th dorsal vertebræ.

Case 18 suffered two injuries: on the first occasion a fall from a horse led to six months incapacity from numbness and weakness of the left arm, and twenty years later the patient was blown up and struck between the shoulders by a sandbag. At the time of examination radiograms showed an old fracture of the 5th dorsal vertebra.

Case 37 injured the cervical spine in a hunting accident and for four weeks experienced paræsthesiæ in the hands on flexing the neck. Radiograms taken ten years later showed an old fracture of the 4th and 5th cervical vertebræ.

Cases 25, 27, 38 suffered injuries to the spine followed immediately by weakness and paræsthesiæ in the limbs which cleared up completely to be followed by a variable latent period before the recurrence of symptoms. In them no evidence of actual fracture was obtained.

Cases 29, 39, 41 experienced no nervous symptoms at the time of the spinal trauma, and no radiological evidence of bony injury was obtained at the time of examination.

In the three cases in which radiograms showed an old fracture, the meningeal changes were confined to the neighbourhood of the damaged vertebræ.

Of the nine cases in which a history of trauma was obtained no other probable ætiological factors could be found in six, but in three cases a history of some form of infection was also present.

Infection.—A history of severe infection in the past was obtained in eight cases. The most convincing evidence that this was responsible for the subsequent meningitis circumscripta was found in Cases 19 and 33, both of whom were young adults who had suffered from proved meningococcal meningitis within two years of the onset of spinal symptoms. In both of these gross arachnoidal adhesions and loculation were found at operation.

In four cases a history of enteric fever from fifteen to thirty years previously was obtained, and in two pneumonia had occurred within two years of the onset of symptoms, but proof of any connection between the infection and the spinal disease is lacking.

Syphilis.—A history of syphilis was obtained in four male cases, the primary infection occurring two years (Case 1), ten years (Case 15), fourteen years (Case 8), and thirty-five years (Case 34) respectively before the development of spinal symptoms. In two cases (1 and 8) no serological investigations were carried out. In Case 15 the earliest symptoms were those of an acute myelitis diagnosed at the time as syphilitic, and when further spinal symptoms developed after an interval of seven years the cerebrospinal fluid showed a lymphocytosis and a weakly positive Wassermann reaction. At the time of operation the cerebrospinal fluid was normal in all respects and the blood Wassermann reaction negative.

Case 34 acquired the primary infection at 20, developed gummatous ulcers of the legs at 27, and spinal symptoms at 52. The Wassermann reaction in blood and cerebrospinal fluid was repeatedly negative, and the latter normal except for slight increase in protein.

It may be questioned whether it is justifiable to include in this series cases in which definite evidence of syphilis was obtained in view of the widespread changes in the cord and its membranes so frequently caused by this disease. But the symptoms and operation findings did not differ from those present in the cases where there was no such history, and even in Case 15, where the patient never made a complete recovery from an early attack of myelitis, there was no serological evidence of active meningeal or vascular syphilis. It seems reasonable to regard syphilis as one of the several conditions capable of giving rise to a low grade inflammatory process in the spinal meninges which in its turn produces the mechanical disturbances of the subarachnoid space which characterize meningitis circumscripta whatsoever its ultimate cause.

Gonorrhœa, to which Horsley attributed some influence in the causation of this disease, had occurred in the past in four male cases without any evidence of a concurrent syphilitic infection. In none of these was there any evidence of the latter disease serologically.

In brief, in forty-one cases of meningitis serosa circumscripta a history of spinal injury was obtained in nine cases, of syphilis in four cases, of meningococcal meningitis in two cases, of gonorrhœa in four cases and of other systemic infections in six cases. In eighteen cases (44 per cent.) no cause whatsoever could be traced.

CLINICAL FEATURES.

As might be expected the clinical picture presented by the disease is very variable. In the first place any part of the spinal cord or cauda equina may be affected; in the second place the process may be strictly localized or diffuse; and finally the onset may be rapid or very gradual.

Although in my cases it was often impossible to assign the symptoms to disease of a single spinal segment we can estimate the site of maximal damage by the level taken to be the centre of the operative field at laminectomy and on this standard it is clear that no portion of the spinal cord is immune to the disorder.

The distribution was as follows:—

High Cervical (C.1-C.4)	6 cases
Cervical enlargement (C.5-C.8)	6 ,,
Upper dorsal (D.1-D.6)	15 ,,
Lower dorsal (D.7-L.2)	9 ,,
Lumbo-sacral enlargement and cauda equina	5 ,,

In discussing the length of history Stookey has stated that the disease has a very gradual onset, and 50 per cent. of his cases gave a history of more than nine years. This is not true of the present series for only three gave a history of more than five years, and of the forty-one cases 53 per cent. had a duration of less than one year and 85 per cent. of less than three years.

In spite of the differences of site, extent, and duration of symptoms analysis shows a considerable background of similarity in my cases.

Two modes of onset of symptoms were commonly encountered, viz. (*a*) spontaneous pain, and (*b*) symptoms of spinal compression, namely weakness or sensory disturbance below a certain segmental level.

Spontaneous pain was the first symptom in twelve cases. The pain was often sudden in onset, and variously described as "stinging," "burning," "gnawing," or "neuritis like." In some cases it was described as "sciatica" or "lumbago." The pain usually began on one side of the body, but later became bilateral. At first it was commonly confined to the cutaneous distribution of one or two spinal segments, but it usually spread until a wide cutaneous area was involved, differing in this respect from the root pain experienced in spinal compression from other causes.

The pain was aggravated by movements of the spine, and in many cases by straining, coughing, and sneezing. Horsley and Mauss and Krüger also comment on the occurrence of diffuse pain.

In twenty-nine cases the first symptoms were those of spinal compression such as might occur in any compressive lesion, and their precise nature was largely dependent upon the part of the cord involved.

In seventeen cases motor symptoms were the first to occur, manifesting themselves by dragging of the legs, weakness of the arms, muscular rigidity, or involuntary spasms.

In eleven cases disturbance of sensation occurred before any motor symptoms, showing itself by numbness, coldness and paræsthesiæ in eight cases, and by clumsiness and inco-ordination in three cases. In one case the first symptom was defective control of the bladder.

Whatever the mode of onset, whether with spontaneous pain or symptoms of compression of the cord, whether rapid or gradual, examination of the patient usually showed well-defined motor, sensory and reflex signs of local disease of the spinal cord and its nerve-roots.

Motor signs.—In no less than thirty-four cases a spastic paraplegia with characteristic changes in the reflexes was found. In twenty-three the upper limbs were quite normal, but in nine there was atrophy and hypotonia of the muscles of the hands and arms, and in two the upper extremities shared the spastic weakness present in the legs.

Of the seven cases in which a spastic weakness of the lower limbs was not present, five cases showed signs of disorder of the lumbosacral enlargement or of the cauda equina, i.e. weakness and wasting of the corresponding muscle groups with diminution or loss of their tendon reflexes.

In two cases motor signs were absent, and the reflexes were normal.

Sensory disturbances.—The commonest type of sensory disturbance was a diminution or loss of cutaneous sensibility below a certain segmental level. This was present in thirty-four cases. In twenty cases this disturbance was bilaterally symmetrical, but in fourteen one side of the body was more affected than the other. The upper level of sensory loss was well defined and identical for all forms of sensation in twenty-three cases, but in eleven cases the level was more irregular, and the sensory disturbance was dissociated. In eight of these cases the loss was more extensive for pain and temperature than for light touch, but in three cases the converse was true.

Cutaneous hyperæsthesia was present in six cases; the hyperæsthetic area was situated immediately above the upper level of sensory loss in three cases, and immediately below the area of chief sensory disturbance in three, and in two cases it corresponded accurately with the area of spontaneous pain.

In four of the cases in which there was not a general diminution of cutaneous sensibility below a certain level, patchy areas of sensory loss were present. They varied in extent, but in all cases the abnormal areas covered the cutaneous field of a number of adjacent spinal segments and were symmetrical, with zones of normal sensibility above and below. In all cases these bands of anæsthesia affected all forms of cutaneous sensation alike and were severe in degree, suggesting that they were due to involvement of the posterior spinal nerve-roots, in contrast to the more uniform loss below a certain level which was found when the changes in sensation were due to medullary lesions. In three cases only was cutaneous sensory disturbance entirely absent.

Deep sensibility, like cutaneous sensibility, was frequently abnormal. The state of postural sensibility and sense of passive movement at joints is recorded in thirty-six cases, and in twenty-one it was disturbed in various degrees. With one exception all these cases showed also a gross loss of cutaneous sensibility in the affected parts. On the other hand fifteen cases presented no defect of postural sensibility in spite of the fact that in all except three of them considerable cutaneous sensory loss was present.

It appears, therefore, that the sense of position and passive movement, as ordinarily tested, are frequently normal in the presence of marked cutaneous sensory loss, but that the reverse is rare.

The sense of vibration at bony points is recorded in twenty cases. In five cases it was absent below a particular level, and in four of these the loss was associated with grave disturbance of postural sensibility, while in one the latter was normal. In eight cases the perception of vibration was diminished but not lost, and in all of these postural sensibility was defective in the same areas. In seven cases the appreciation of vibration was normal, and in all of these postural sensibility was also unaffected, although in some cutaneous sensory loss was present. These observations suggest that vibratory loss is associated with loss of sense of position and is unlikely to appear as an isolated phenomenon.

Function of the cranial nerves.—The state of the cranial nerves was recorded in thirty-nine cases, and was normal in thirty. In four cases slight pupillary abnormalities were noted. In Cases 3 and 6 this consisted of slight inequality in size without any other departure from normal. In Case 10 the pupils were unequal in size and the left was irregular in outline and reacted sluggishly to light. There was no other evidence of syphilis. In Case 34, who gave a history of syphilitic infection, one pupil reacted poorly to light. In five there was a slight degree of nystagmus. This was never sustained and was usually described as "slight nystagmoid jerks on full lateral deviation of the eyes." In one case mild signs of ocular sympathetic weakness were present on one side.

Disturbance of the sphincters.—The state of the organic reflexes is recorded in all cases. In fourteen they were normal, in spite of the fact that many of the patients had moderately severe paraparesis. In twenty-four cases early sphincter disturbance was present, showing itself variously as a delay in starting, precipitance, or occasional incontinence. In only three cases was loss of sphincter control a marked feature, and in all of them a severe paraplegia was present. The sphincter disturbance is thus mild when compared with the severity of the motor and sensory changes.

Trophic changes.—Cutaneous lesions and bed sores were strikingly rare, and were only noted in three cases. In one the marks of a bottle burn were present, and in two there was evidence of old bed sores at pressure points. Horsley noted the late appearance of sphincter and trophic disturbances in this condition.

Vertebral column.—A record of the clinical examination of the spine was obtained in thirty-seven cases. In ten cases some abnormality was detected clinically, of which tenderness on pressure and percussion of the vertebral spines in the affected area was the commonest and was present in six cases. In five cases spinal rigidity was described. X-ray examination in those cases where there was clinical evidence of spinal abnormality showed arthritis in three cases, an old vertebral fracture in one case and diminution of an intervertebral space in another. In twenty-seven cases clinical examination revealed no evidence of spinal abnormality, but in spite of this radiograms showed an old fracture in one case, spinal arthritis in another, and doubtful erosion of one vertebra in a third.

PATHOLOGICAL INVESTIGATIONS.

The Wassermann reaction of the blood was determined in twenty-seven cases and was completely negative in twenty-six. These cases included four with a history of syphilis and four with one of gonorrhœa. In one case (Case 13) it was weakly positive, although no history or other signs of syphilis were present.

Cerebrospinal fluid.—Changes in the cerebrospinal fluid in cases of meningitis circumscripta spinalis have been described by several writers, but usually in reports of isolated cases. Stookey, in his series of thirteen cases, found manometric evidence of a complete subarachnoid block in six cases and of a partial one in four cases. In none was xanthochromia present.

On the other hand a complete Froin's syndrome was present in the cases described by Grinker, Hiller, and Guillain, and in one of Vincent's cases. In ten of Stookey's cases the cell-count was normal, but in three a pleocytosis was present, the cell-counts being 14, 12 and 6 lymphocytes respectively. Other authors have found moderate increase in the number of cells; Kron's case had 72 cells per c.mm., Vincent's cases 20 and 9 cells per c.mm. respectively, and that of Skoog 9 per c.mm. The majority of case reports in the literature, however, are in agreement in the absence of any increase of cells in the spinal fluid. All writers have found the Wassermann reaction in the cerebrospinal fluid uniformly negative.

In the present series the cerebrospinal fluid was examined in twenty-six cases although in some of the earlier ones the analysis was incomplete as judged by modern standards. In three cases fluid was unobtainable, and in twelve no attempt was made to obtain it. Manometric examination was carried out in only six of the forty-one cases. A complete block was present in one case in which the protein content was 0·11 per cent. A partial block was found in two cases with protein contents of 0·08 and 0·16 respectively. In three cases the pressure relationships as measured by the manometer were normal.

The cells were enumerated in each of the twenty-six cases in which the spinal fluid was obtained—and with one exception the count was normal (less than 5 per c.mm.). In one case counts of 50 and 42 lymphocytes per c.mm. were obtained on successive occasions, although there was no history of syphilis and the Wassermann reaction was negative in blood and fluid.

The total protein content was estimated in twenty-one cases and was normal (less than 0·05 per cent.) in eleven of them. In four cases it was slightly raised (0·05 to 0·08 per cent.), and in five cases there was a gross excess of protein (0·14, 0·2, 0·85, 0·11, 0·16 per cent.). The cases with great excess of protein all showed other evidence of loculation (i.e. yellow coloration, a positive Queckenstedt's phenomenon or arrest of lipiodol). Qualitative tests for globulin showed an increase proportional to the excess of total protein. It seems, therefore, that in meningitis serosa circumscripta marked increase in protein only occurs as a result of occlusion of the subarachnoid space This is in agreement with the observations of Vincent and Stookey.

The Wassermann reaction was examined in the cerebrospinal fluid in twenty-five cases and in all it was negative. One case (Case 15) had given a weakly positive reaction on a previous occasion, but this was not confirmed at the time of examination.

The Lange colloidal gold sol reaction was carried out in thirteen cases and was normal (no rise above 2 in any dilution) in twelve. In one case in which there was a total protein content of 0·2 per cent. a meningitic curve was obtained.

Lipiodol examination.—Attention has been drawn by Barré, Hiller, Moniz, Marinesco, and Paulian and Turnesco to the striking features presented in radiograms of the spine in cases of meningitis circumscripta after the introduction of lipiodol into the cisterna magna.

While in cases of spinal compression from other causes the opaque oil is held up in its entirety at the level of the spinal lesion, these authors find that in the presence of diffuse arachnoidal adhesions the lipiodol is arrested in droplets over a considerable extent above the site of the main lesion, giving an appearance reminiscent of a guttering candle. At the same time the arrest is incomplete and some of the oil is seen in the sacral end of the subarachnoid space.

The illustrations in the monograph of Paulian and Turnesco show this patchy arrest very clearly, but this appearance is by no means always present in otherwise characteristic cases. In cases reported by Guillain and by Vincent the whole of the opaque oil was arrested in one mass as in cases of tumour. On the other hand the writer has seen a widespread arrest of lipiodol in droplets of varying size in a case of diffuse vascular tumour of the cord.

In the present series lipiodol was introduced into the cisterna magna in seven cases only. In five it was arrested at a single level, which in each case was found at operation to be the site of marked abnormality of the subarachnoid space. In two cases the oil descended normally to the bottom of the subarachnoid space. The diffuse arrest referred to in the literature was not seen.

DIAGNOSIS.

Spiller in 1909 and Horsley in the same year stated that meningitis serosa circumscripta spinalis resembled closely in its symptomatology spinal compression from tumour, and that it was usually diagnosed as such before operation. Careful examination of the present series amply confirms this statement, for the correct diagnosis was seldom suggested before operation, and even more rarely put forward with any degree of certainty. In spite of the improvement in accessory investigations it is probably equally true to-day.

Indeed it is difficult to see how a certain diagnosis of meningitis serosa circumscripta spinalis can be made before operation, particularly when one remembers how frequently spinal tumours, especially vascular ones, are associated with arachnoidal adhesions above and below the lesion. There are, however, certain features which should raise the possibility of this diagnosis in the clinician's mind when faced with a probable case of spinal compression. The disease as has been shown is predominantly one of middle age and a history of definite spinal trauma, of past infection of the subarachnoid space or of syphilis is of value.

Though the more common mode of onset is that of an insidious spinal compression the commencement with spontaneous pain, when it occurs, is highly suggestive. This pain may be of sudden onset and is usually intense and intractable, and is diffuse in its distribution and frequently associated with hyperæsthesia. On examination the patient usually shows signs of a localized spinal compression together with a more diffuse involvement of the spinal nerve-roots. The root symptoms tend to be more conspicuous than in spinal tumours, whereas the spinal compression is slow in reaching an extrême degree so that trophic changes and disturbance of the sphincters are long delayed.

Unfortunately examination of the cerebrospinal fluid does not serve to distinguish the condition from spinal compression due to other causes. The value of lipiodol examination, as has been said, is stressed by French authors and certainly the diffuse patchy arrest of the oil over a wide area of the subarachnoid space when it is seen is highly suggestive of widespread adhesions in the subarachnoid space. This appearance may however be absent in cases of meningitis circumscripta and may be present in other conditions. It will thus be seen that while there are many points of value in the differential diagnosis between meningitis serosa circumscripta and other forms of spinal compression, there are no absolute diagnostic criteria.

It is true to say that the diagnosis can only be suspected and not established before operation.

PATHOLOGY.

The nature of the lesion present in cases of meningitis serosa circumscripta may be studied both from the findings at operation and by the more searching methods of biopsy and post-mortem examination. The former source is comparatively plentiful but the latter is unfortunately scanty.

Previous writers are in general agreement that the most conspicuous abnormalities seen at operation are to be found in the arachnoid. This membrane is unusually thick and often opaque in appearance. It is bound to the dura and to the cord and nerve-roots by adhesions which vary greatly in their number and extent. They may be localized or diffuse and often interfere with the normal circulation of the spinal fluid so that cysts are formed. In extreme cases they may be so extensive as to obliterate altogether the subarachnoid space

Many authors draw attention to the great tension under which the fluid is contained within the arachnoid cysts and refer to the distended appearance of the dura and its feeble pulsation. The appearances of the arachnoid are admirably portrayed in a series of coloured plates in the paper of Mauss and Krüger.

The changes seen at operation, however, are not always confined to the arachnoid. In some cases the dura is thickened, and in the traumatic cases of Mauss and Krüger the epidural space contained organizing blood-clot and the epidural fat was undergoing fibrosis. Again changes in the spinal cord and its nerve-roots are frequently mentioned. Horsley was particularly impressed by the shrunken appearance of the cord. Skoog noted compression of the cord as if by an extramedullary tumour, and Bliss refers to changes in the pial circulation.

The present material confirms the previous findings and is of particular value as all the cases (forty-one) were submitted to laminectomy and with four exceptions the operations were performed by the same surgeon. In many cases his notes made immediately after the operation are available and are at times quoted verbatim.

Changes in the superficial tissues and spinal laminæ were noted in only five cases. In three, bony thickening was found at the site of an old fracture; in one case œdema, and in another fibrosis of the spinal muscles was present. In many cases (sixteen) the dura mater was recorded as being normal in appearance, but in some (eleven) it was noticed that the normal pulsations were greatly diminished or absent; in five cases the dura was found to be abnormally thick, and in some it was unusually tense on palpation.

It was on opening the dura, however, that the most striking and constant changes were seen. In eleven cases there were abnormal adhesions binding the inner surface of the dura to the arachnoid. The arachnoid itself was often milky and opaque in appearance, and in some the thickening had a patchy distribution. Of Case 3 it is noted that "the posterior surface of the cord showed alternate grey and white patches and there were small opaque areas in the pia like minute gummata," and of Case 8 that "the arachnoid was greatly thickened and appeared like flakes of lymph in peritonitis."

The most constant finding was the presence of abnormal adhesions between the arachnoid and the pia with consequent disturbance of the subarachnoid space. These adhesions were specifically noted in twenty-seven cases. They varied greatly in number and extent. In some they were strictly localized as in Case 15, where "at the 6th dorsal segment there was an incomplete septum between the arachnoid and the posterior surface of the cord," and in Case 35 in which "a firm band of opaque arachnoid extended up and down for ¾ inch, constricting the cord at the level of the 4th cervical lamina." In other cases the changes were spread over a considerable length of the cord.

In association with the arachnoidal adhesions there occurred in eighteen cases loculated collections of fluid amounting to actual cysts. In four cases these were single, in two they were multiple, while in the remainder there was "a cystic loculation of fluid" without specification as to whether there were one or more cavities. In most cases the contained fluid was under pressure and escaped in a sudden gush on puncturing the cyst wall, leaving a depression on the surface of the cord as if a tumour had been removed, and in some cases permitting the return of a previously displaced cord to its normal position.

The spinal cord itself was frequently described as having an abnormal appearance. The most frequent change was a decrease in the normal vascularity of the pia, and in some instances the breaking down of the arachnoidal adhesions led to an immediate return of the normal pial circulation. In some cases, on the other hand, engorgement of the pial veins was seen. Shrinkage in size of the spinal cord was commented on in six cases.

The posterior spinal roots showed abnormal appearances in six cases, the most striking being a matting together of the roots by arachnoidal adhesions; this was particularly noticeable where the cauda equina was involved. In some cases the nerve-roots appeared shrunken, and in others they were swollen, hyperæmic, and beaded in appearance.

To summarize these observations: Operation commonly showed a dura mater which pulsated defectively and a thickened arachnoid bound by adhesions to the overlying dura and more often still to the underlying pia. These arachnoidal adhesions were in some instances associated with solitary or multiple cysts, which in their turn compressed the cord. Further, the adhesions often disturbed the normal vascular arrangement of the cord; then the latter presented a pale, shrunken appearance.

The following operation notes illustrate the changes seen on laminectomy:—

Case 10.—"The arachnoid from end to end of the incision was uniformly thick and opaque, looking like a wet blanket enveloping the cord. On incising it, clear cerebrospinal fluid escaped. The cord appeared pale and shrunken, and yet the arachnoid was only slightly adherent to it. The thickening of the arachnoid involved the covering of the roots and of the ligamentum denticulatum."

Case 11.—"Adherence of the arachnoid to the dura prevented the exposure of the former without escape of cerebrospinal fluid. After opening the dura the cord was seen to be pushed backwards by something lying anterolaterally and presenting between the 6th and 7th dorsal roots on the right side. On probing this there was a sudden gush of fluid from what appeared to be a tense cyst. The cord immediately sank back, assuming a normal appearance and pulsating naturally."

Case 15.—"The arachnoid appeared normal, but was very tightly distended with cerebrospinal fluid. There was no evidence of loculation, but at the level of the 6th dorsal segment there was an incomplete septum between the arachnoid and the posterior surface of the cord. The cord was pale and shrunken and the pia remarkably devoid of blood-vessels."

Case 19.—"The membranes were all matted and there was no general subarachnoid space. The nerves of the cauda equina were matted into a solid bundle. Opposite the arch of the 10th dorsal vertebra on the left side there was a cyst with a fairly thick wall, fusiform in shape and some 1½ in. long. It lay on the left of the cord which was compressed exactly as by a tumour. After emptying the cyst the cord was 'cupped' and it expanded considerably during the rest of the operation."

Case 35.—"On opening the dura an opaque band of arachnoid was found constricting the cord at the level of the 4th cervical vertebra and extending up and down for ¾ in. When it was severed the cord, which was previously constricted in that region, regained its normal vascularity."

The literature contains but few cases which were submitted to a careful autopsy, or in which tissue removed at operation was examined microscopically.

Grinker [19] describes a case of meningitis serosa circumscripta in which the lumbo-sacral enlargement and cauda equina were involved, and which died after operation. At autopsy the spinal leptomeninges appeared slightly thickened and opaque. The cord appeared normal except in the conus medullaris which was soft. The cauda equina was normal except for dilatation of its veins. Microscopically the cord showed no evidence of tumour, cavitation or collections of unusual cells. Weigert preparations and sections stained for fat were normal, but Nissl preparations showed some chromatolysis in the cells of the lumbo-sacral enlargement. The pia mater was normal, but the arachnoid and perineurium were severely altered. They were thickened by increase of connective tissue, the blood-vessels were dilated and the tissue contained excess of pigment. There was no perivascular infiltration with leucocytes.

Kron [21] describes a case in which some of the small opaque areas found in the arachnoid at operation were excised for microscopy. They consisted of piled-up layers of connective tissue in interlacing bundles of unequal size. In places there was a rich round-celled infiltration.

Marinesco, Draganesco and Hornet [28] describe the post-mortem findings in a case in which the lumbo-sacral enlargement and cauda equina were involved in a patient giving a past history of syphilis. The patient died eighteen months after operation. Microscopically the dura appeared normal. The pia-arachnoid was a little thickened in the mid-dorsal region and greatly so in the region of the lumbo-sacral enlargement and cauda equina. It was adherent to the dura and contained a number of small milky plaques. The cord itself was atrophic in its lower part. Microscopically the dura was normal but the pia-arachnoid was greatly thickened. The fila of the cauda equina appeared as if embedded in celloidin. The newly formed tissue consisted of fibroblasts infiltrated with lymphocytes and contained proliferating blood-vessels. There was thickening of the adventitia of the vessels and hyaline degeneration of their walls. The cauda equina showed some increase in the number of nuclei of the sheath of Schwann. The cord itself had suffered some peripheral demyelinization in the lumbo-sacral region, and an area of softening with degeneration of the ganglion cells was present at the 10th dorsal segment.

My own material for microscopical study is unfortunately scanty and adds little, if at all, to our understanding of the cause of the disease.

It consists of material removed at operation in two cases (35 and 41) and full microscopical examination of the cord removed at autopsy in one case (32).

Case 35.—Portions of the opaque bands of arachnoid, found at operation to be constricting the cord, were removed. Microscopically they were found to consist of hyaline connective tissue with an inner layer of endothelial cells. The connective tissue was very much thicker and less cellular than the normal arachnoid, and in one or two places its fibres were formed into rounded knots of hyaline material. There was no cellular infiltration.

Case 41.—Portions of the spinal muscles, extramedullary fat, dura mater and arachnoid were removed for examination. The muscle fibres were normal except that chains of nuclei were seen at the insertion of several fibres. One or two areas of dense lymphocytic infiltration were present in the perivascular lymphatics. The extramedullary fat, dura, and arachnoid appeared normal.

Case 32 (*Summary*).—Male, aged 52. Nine months' history of increasing weakness of legs and paræsthesiæ of arms. Signs of spinal compression at C.4 segment. Cerebrospinal fluid was at first normal, later showed increase of protein. Laminectomy revealing arachnoidal cyst. Death. Autopsy.

H. B., a male boot operative, aged 52, was admitted to the National Hospital, Queen Square, under the care of Dr. Holmes, on April 4, 1929. He complained of weakness of the legs of nine months' duration. He had acquired gonorrhœa in his youth and twenty years before had suffered an attack of sciatica on the right side which had cleared up after nine months and had not recurred. Three years before admission he had several carbuncles. In other respects his past health has been good and his family history was uneventful.

His illness began nine months before admission with involuntary spasms of the legs at night. Three months later the legs became numb and tingling after walking, and his gait became unsteady, especially in the dark. At this time a purulent discharge occurred from the right ear, followed by deafness on that side. Two months before admission his legs began to tremble, and one month later a numb sensation began in the fingers of both hands and spread up the arms. Slight delay in starting micturition was noticed, but there were no other symptoms.

On examination the functions of the cranial nerves were normal except for deafness in the right ear from chronic otitis media and slight nystagmoid jerks on full lateral deviation of the eyes to right and left.

There was slight general atrophy and weakness of the muscles of both arms but especially of the triceps. Fibrillation was seen in the deltoid and triceps of the left side. The musculature of the trunk was normal, that of both lower limbs showed slight general weakness.

The tendon reflexes were symmetrically accentuated throughout the body, the abdominal reflexes were diminished on the right and absent on the left, and both plantar responses were extensor.

Sensibility to pin-prick was diminished along the ulnar borders of both hands, forearms and arms and upon the trunk from D.2 to D.8 segments and D.10 to D.12 segments, and on the legs below the middle of the thighs. Sensibility to light touch and temperature was everywhere normal, and the appreciation of passive movement and vibration and compass point discrimination were undisturbed. His gait was ataxic.

The cerebrospinal fluid contained 0·05 per cent. protein and 2 cells per c.mm. Qualitative tests for globulin were negative, as was the Wassermann reaction. Lange's colloidal gold curve was 0001210000. The pressure of the fluid was not estimated. The blood Wassermann reaction was negative. The blood-count was normal. An X-ray of the spine showed some osteo-arthritis. Under observation the wasting and weakness of the upper extremities increased, while the legs became more spastic. The areas of hypalgesia extended until there was a general diminution below C.7 segment on the right and C.8 on the left. Lipiodol was introduced into the cisterna magna and descended normally.

The patient was discharged to be kept under observation, but was readmitted on May 27. The symptoms had steadily increased. The paræsthesiæ in hands and arms were more severe and the legs weaker. Considerable pain was experienced in the lower abdomen and the thighs.

The wasting of the hands and forearms was more evident and the sensory loss to pin-prick had extended up to the C.3 segment and there was diminution of sense of temperature and light touch below C.4 segment. The cerebro-spinal fluid was again examined. The initial pressure was 200 mm. Queckenstedt's test negative. Total protein 0·85 per cent. Cells 4 per c.mm. Globulin was present in excess. The Wassermann reaction was negative in blood and fluid.

The diagnosis of intramedullary tumour was considered most likely, but syringomyelia and meningitis serosa circumscripta were considered as alternatives. It was decided to explore the spinal cord with C.3 and C.4 segments as the centre of the operative field.

On June 21, 1929 laminectomy was performed, the laminæ of the cervical vertebræ 1 to 5 inclusive being removed. The dura was tense and filled with spinal canal but it pulsated normally. It was opened without injuring the arachnoid which was quite translucent—without any opacities.

The cord was seen to be pushed backwards and a probe was passed in front of the cord without injuring the visible portion of the arachnoid. Immediately there was a gush of clear fluid and the cord resumed its normal position. The arachnoid still surrounded the cord as a translucent distended membrane and no blood entered its spaces. The condition was considered to be one of meningitis serosa circumscripta and the wound was closed in the usual way.

The patient died two days later from bronchopneumonia and a partial post-mortem examination was made as removal of the brain and spinal cord only was allowed. The brain appeared to be normal in every way. The spinal cord was distorted in shape at the level of the 4th cervical segment in such a way as to suggest that it had been compressed from its right lateral aspect. Below this level the cord was normal in appearance and no alteration in the pia or arachnoid could be detected in any part. The cord was fixed in 10 per cent. formol saline and sections of each spinal segment prepared and stained by Weigert's method and with haematoxylin and van Gieson's stain.

Weigert preparations.—In segments C.1, C.2, C.3 there was marked distortion of the normal shape of the cord which was flattened from side to side. There was a marginal zone of pallor in each lateral column and the bundles of myelinated fibre were broken up as if from trauma.

The most striking change, however, was seen in the posterior columns. The columns of Goll were well preserved but on both sides there was a band of pallor in the columns of Burdach in their medial part, which began near the periphery and extended in increasing intensity towards the posterior grey commissure. In the more anterior part the areas of degeneration on either side converged towards the mid-line until they reached the postero-median septum and the posterior grey commissure.

The descending tracts in these segments stained normally. In the 4th cervical segment the changes were more marked. The band of degeneration in the columns of Burdach had become more intense and there was pallor of one column of Goll. The entering posterior roots showed demyelinization but the descending tracts were preserved.

At C.5 the cord had assumed its normal contour. The areas of degeneration in the columns of Burdach persisted and the entering posterior roots showed marked pallor. The columns of Goll were normal and apart from a marginal zone of pallor the anterior and lateral columns were unchanged.

At C.6 the picture had changed. The areas of degeneration in Burdach's columns had almost disappeared except near the posterior grey commissure. The entering roots appeared normal. There was now marked pallor in the lateral columns especially in the zone occupied by the pyramidal tract and to a less degree throughout the antero-lateral white columns. The appearance of C.7 and C.8 were similar and in D.1 segment the pallor of the lateral columns and on either side of the anterior median fissure was very marked. In this section, however, the posterior roots again showed degeneration and there was a circumscribed area of pallor, almond shaped, in each column of Burdach.

These areas grew less evident in the sections of segments D.2 and D.3 and from D.4 to D.7 the picture was that of an uncomplicated descending degeneration. The posterior columns stained normally, the pyramidal tracts showed marked pallor and the antero-lateral columns a slight degree of demyelinization.

These changes persisted throughout the lower segments of the cord, but at D.8 a small area of pallor was to be seen in one column of Goll in the immediate vicinity of the posterior median septum. This area increased in size as the cord was descended until D.11 segment but afterwards decreased until the S.3 segment where it disappeared.

The appearance of the sections stained by Weigert's method suggest that the cord had been subjected to compression which was most intense at the 4th cervical segment. Above this level there was degeneration of the ascending tracts, below it of the descending tracts. In addition over several segments of the cervical cord the incoming posterior roots showed degenerative changes.

Sections of each spinal segment were stained with hæmatoxylin and counterstained by van Gieson's method. There was no abnormal thickening of the pia at any level and the blood-vessels throughout appeared normal. There was no cellular infiltration of the leptomeninges and no increase of cells in the perivascular spaces of the cord.

The substance of the cord itself appeared normal at all levels except in the upper cervical region at which there was some marginal rarefaction of the white matter where fibres had disappeared with very little glial proliferation. The nerve-cells of the cervical and lumbar enlargements were normal.

The pathological findings in this case are such as might be expected in any case of spinal compression above the cervical enlargement and cannot be said to add any positive facts to our knowledge of the nature of meningitis circumscripta. Taken in conjunction with the clinical and operation findings they do however show that severe spinal compression may be caused by an extremely local change in the pia-arachnoid without any change being detectable in the remainder of the cord or its membranes.

Consideration of the operative findings and of the pathological material available from the present cases and from the descriptions in the literature, leaves little doubt that the essential change in meningitis serosa circumscripta is a morbid process in the spinal leptomeninges, whereby abnormal adhesions and bands are formed in the subarachnoid space which may or may not be associated with cystic accumulation of fluid in their meshes.

These adhesions owe their existence to a low-grade inflammatory process which is probably of diverse origin. They vary in degree from single bands and diffuse fine strands of fibrous tissue to dense adhesions obliterating the subarachnoid space and enveloping the emerging nerve roots. From whatever cause the meningeal adhesions arise they produce their symptoms by disturbing the functions of the spinal cord or its nerve-roots by direct mechanical pressure and by interference with the vascular supply of the cord which leads in its turn to intramedullary changes.

Stookey has suggested that the intramedullary changes result from the repeated minor traumata which are inflicted upon an anchored cord by the normal spinal movements, but this theory seems to have no advantages over the simpler one of medullary ischæmia, and it fails to explain convincingly those cases where the process remains strictly localized.

Post-operative Course of the Disease and Prognosis.

The prognosis in cases of meningitis circumscripta has been the subject of widely differing estimates by those who have written on the subject. In many isolated cases, particularly where a localized cystic change was found, complete recovery has followed relief of the spinal compression. Horsley considered that the prospect of recovery was good in middle-aged subjects, but poor in the elderly. Stookey considered the prognosis to be favourable if all the adhesions could be severed. Vincent found it to be variable, and stated that when intramedullary changes had occurred little improvement could be expected from operation.

In order to throw light on this aspect of the subject an attempt has been made to trace the subsequent history of the patients referred to in this paper. A record up to the time of death, or until 1935, has been obtained in twenty-four cases. The remaining eighteen cases have been lost sight of at varying intervals after their operations.

Of the twenty-four cases whose subsequent course is completely known five died within three weeks of their operation and may be regarded as direct operative deaths. Eight cases are known to be now dead. Four of them lived less than one year, one survived three years, others nine and ten years respectively. In one case the date of death is unknown. Eleven cases are known to be alive. Of these, four are the same or worse than at the time of operation, and are incapacitated by their disease, but seven have made a complete recovery and are able to work with minor disabilities in some cases. The periods which have elapsed since their operations are fifteen, twelve, eight, eight, seven, five and four years respectively, so that it seems reasonable to regard their relief as a cure. Thus in only seven out of these twenty-four cases (29·2 per cent.) could the outcome be regarded as satisfactory.

It is much more difficult to assess the outcome of the seventeen cases of which trace has been lost. In five of them no information is available. Three, when last heard of, were the same or worse than at the time of operation. Nine cases when last heard of were better than at the time of operation, and in five of these the observation was made two or more years after the operation and may be regarded as satisfactory evidence of recovery. In four cases the period of observation was too short to permit of reasonable judgment.

Thus in the seventeen cases ultimately lost sight of there is reason to think that the outcome was favourable in five (29·4 per cent.), which agrees closely with the more accurate figures available in those cases where full records are available.

The twelve cases (seven certain and five probable) in which the outcome was favourable have been examined to see if there is any common feature which may indicate a good prognosis. Possible underlying causes did not appear to influence the prognosis. In two cases there was a history of syphilis, in two of some other infection, while in six no causal factor could be ascertained.

The duration of the illness before operation was of more significance. In eight of the twelve favourable cases symptoms had been present for less than one year, while in only one had they been present for more than three years. The average duration of these cases before operation was

11·5 months, compared with 24·9 months of the whole group, suggesting that a short pre-operative history is a favourable feature in the prognosis.

The changes found at operation are also an important indication of the probable outcome. In all twelve cases diffuse or localized arachnoidal adhesions were present, in four there was definite cyst formation, and in three a single arachnoid band was found constricting the cord. In none of them was there described any abnormality in the appearance of the cord itself (e.g. pallor or shrinkage), and in several it was specifically stated that the cord appeared normal. It seems, therefore, that the cases which do well share in common the fact that there were no visible changes in the spinal cord itself. On the other hand five of the six cases in which the cord was shrunken had an unfavourable outcome, and none of the cases in which pallor of the cord or avascularity of the pia were noted at operation appear in the group of cases which did well.

Obvious changes in the spinal cord at operation thus indicate a grave prognosis.

SUMMARY.

(1) The clinical and operative findings of forty-one cases of meningitis serosa circumscripta are analysed.

(2) While the pathogenesis is often obscure it is suggested that trauma, meningeal infections, and syphilis are among the causes.

(3) The essential change is the development of adhesions and cysts in the spinal subarachnoid space which produce secondary intramedullary changes by compression and ischæmia.

(4) The symptoms and signs closely resemble those of spinal compression by tumour, but certain points of value in the differential diagnosis are noted.

(5) The prognosis must be regarded as grave, but is least so in those cases which are operated on early before irreversible changes have occurred in the cord itself.

REFERENCES.

[1] Spiller, W. G., Musser, J. H., and Martin, E. *Univ. Penn. Med. Bull.*, 1903, **16**, 27.
[2] Bruns, L. *Berlin klin. Wchnschr.*, 1908, **45**, 1753.
[3] Mendel, K., and Adler, S. *Ibid.*, 1908, **45**, 1596.
[4] Bliss, M. A. *Journ. Amer. Med. Assoc.*, 1909, **52**, 885.
[5] Spiller, W. G. *Amer. Journ. Med. Sci.*, 1909, **137**, 95.
[6] Horsley, V. *Brit. Med. Journ.*, 1909, **1**, 518.
[7] Mills, C. K. *Journ. Nerv. and Ment. Dis.*, 1910, **38**, 588.
[8] Weisenburg, T. H., and Muller, G. P. *Amer. Journ. Med. Sci.*, 1910, **140**, 719.

[9] Munro, L. *Surg. Gyn. and Obstet.*, 1910, **10**, 285.
[10] Kennedy, Foster. *Journ. Nerv. and Ment. Dis.*, 1911, **38**, 689.
[11] Bouché, G. *Rev. Neurol.*, 1914, **22**, 69.
[12] Skoog, A. L. *Journ. Amer. Med. Assoc.*, 1915, **65**, 394.
[13] Batten, E. F. *Proc. Roy. Soc. Med.* (Neur. Sect.), 1916, vol. **9**, pt. 2, 63.
[14] Marburg, O. *Wien. med. Wchnschr.*, 1919, **69**, 47.
[15] Mauss, T., and Kruger, H. *Deutsche Ztschr. f. Nervenheilk.*, 1918, **62**, 1.
[16] Bausamer, H. *Med. Klin.*, Berlin, 1920, **16**, 802.
[17] Moniz, E. *Rev. Neurol.*, 1923, **39**, 657.
[18] Barré, J., *et al.* *Ibid.*, 1925, **1**, 604.
[19] Grinker, R. R. *Journ. Nerv. and Ment. Dis.*, 1926, **64**, 616.
[20] Hiller, F. *Mit. a. d. Grenzgebiet. d. Med. u. Chir.*, 1926-28, **40**, 73.
[21] Kron, S. *Zeitschr. f. Nervenheilk.*, 1927, **98**, 295.
[22] Stookey, B. *Arch. Neur. and Psych.*, 1927, **17**, 151.
[23] Hassin, G. B., and Andrews, E. *Journ. Amer. Med. Assoc.*, 1929, **92**, 877.
[24] Vincent, C., *et al.* *Rev. Neurol.*, 1930, **1**; 577.
[25] Guillain, G., *et al.* *Ibid.*, 1932, **1**, 516.
[26] *Idem.* *Ibid.*, 1932, **1**, 908.
[27] Moniz, E., *et al.* *Ibid.*, 1933, **40**, 997.
[28] Marinesco, G., *et al.* *Ibid.*, 1934, **16**, 821.
[29] Paulian, Dem. and Turnesco, D. "Les Arachnoidites Spinales Adhesives" Paris, 1933.

SPINAL COMPRESSION CAUSED BY ECCHONDROSIS OF THE INTERVERTEBRAL FIBROCARTILAGE: WITH A REVIEW OF THE RECENT LITERATURE.

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INTRODUCTION.

DURING the last few years a fair number of cases of spinal compression due to cartilaginous outgrowths of the vertebral discs have been reported. While working at the National Hospital I had the opportunity of studying three such cases, and by the kind permission of the medical staff I have been able to search the records of the Hospital and to present here ten unreported cases. Fifty odd cases have been also selected from the literature, and on this material an attempt has been made to furnish a systematic analysis of the pathology and the clinical features of the condition.

At odd times cases of spinal compression due to large cartilaginous growths arising from the vertebræ or invading the spinal canal from neighbouring structures have been reported. These growths, which were usually multiple and associated with similar easily palpable subcutaneous growths, are not to be confused with those discussed in the present article, which are small tumours arising from the intervertebral discs, usually slightly lateral to the midline, remaining behind the median longitudinal ligament and the dura, varying in consistency and composed of cartilage, fibrocartilage or tissue analogous to the nucleus pulposus, and under certain circumstances becoming calcified or ossified. These have been described under various names as enchondroma, cartilage nodes, fibrocartilaginous extensions of the disc, ecchondrosis and herniation of the nucleus pulposus.

One of the first references to any type of chondroma compressing the cord is in Oppenheim's textbook [1], where he states that Sich, in 1904, removed a spinal chondroma. About 1911 Middleton and Teacher [2], in Scotland, and Goldthwaite [3], in America, recorded cases of spinal compression due to changes in the intervertebral discs. It is interesting how many years passed before similar cases were reported. Potel and Veaudeau [4], in their review of spinal tumours in 1913, mentioned only two, Delaginière [5] in his thesis of 1923 reported but two, and Elsberg [6], in 1925, one only.

It is probable that to Stookey [7] the most credit for the presentation of this condition as a clinico-pathological unit should be given. From the time of publication of his article in 1928 many cases have been reported and a fairly large amount of literature written. Other pioneers in this field were Schmorl and Andrae, who in 1929 published the results of routine post-mortem examinations and brought forth the idea of herniation of the nucleus pulposus as the underlying cause. Since then numerous writers have supported this theory, until at the present time it is definitely the accepted one.

Anatomy.—The vertebral bodies, as described in "Gray's Anatomy," articulate with each other in a simple fashion; between them is a pad, the intervertebral disc, and they are held together by that structure and two longitudinal ligaments, the anterior and the posterior. In the cervical region the latter ligament is broad and of uniform width; in the thoracic and lumbar region it is denticulated, being broadest over the disc and narrowest over the vertebral bodies.

The intervertebral discs form the chief bond of union, adhering firmly to the thin layer of hyaline cartilage which covers the adjacent surface of the vertebræ and uniting with the longitudinal ligaments. Each is composed of a peripheral area of fibrocartilage and fibrous tissue called the annulus fibrosus. In the central portion, and posterior to it, lies a soft, pulpy, highly elastic tissue which is expansile and bulges on section; this is called the nucleus pulposus.

The cartilage lining the vertebræ is hyaline with a clear matrix, containing little groups of two to eight cells surrounded by a deeply staining capsule [11]. The annulus is composed of fibrocartilage; it looks much like fibrous tissue embedded in a uniform matrix, but the cells are true cartilage cells, not fibroblasts.

The nucleus pulposus, according to various authors [12, 13, 14, 15], acts as a buffer and a shock-absorber to the spine; it is composed of 75 to 90 per cent. of water, being a semifluid substance containing loose, fibrous tissue and fibroblasts, normal and degenerating cartilage cells, and peculiar large cells derived from the notochord—the "phylasides of Virchow." The latter are masses of cells with large vacuoles containing glycogen in their cytoplasm and often as many as six to eight nuclei.

Frequency.—The incidence of any lesion is not proportional to the number of cases reported in the literature. More interest and a greater refinement of technique will bring forth many cases which would have been missed under earlier conditions. Indeed, very few are noted in the earlier literature—in a series of 300 verified spinal cord tumours in 1913 [4] there were 107 tumours arising from the vertebræ and only 2 per cent. of these were benign chondromata. In another series of 330 cases collected in Philadelphia, Steinke [17], in 1918, found 14 per cent. were primary vertebral tumours, and of these 50 per cent. were sarcomata. However, in his review he presents six cases of endochondroma, approximately 2 per cent., but he gives no details regarding them. In the next series of note, that by Elsberg in 1925 [6], we find that 20 per cent. were extradural tumours with only one chondroma. However, in his next publication, during 1931, he recorded 40 per cent. of extradural tumours, and 14 per cent. of these chondromata. During the last few years several articles have appeared dealing with this condition, the most important being those by Stookey [7] reporting seven cases, Elsberg [18] reporting fourteen, and Mixter and Barr [12] nineteen. In all, fifty to sixty cases are reported in different articles; as far as their frequency can be estimated the figure of 14 per cent. of all spinal cord tumours is probably too high, it probably lies between 5 and 10 per cent.

Little was known of the intervertebral disc until Schmorl [8] routinely removed the spine at autopsy. In 2,000 cases he discovered 737 cases in which the disc cartilage herniated either into the structure of the vertebræ or posteriorly under the longitudinal ligament. This work was confirmed to a great degree by Andrae [9], who found in 368 autopsies posteriorly-directed extensions of the disc into the spinal canal, in 15 per cent., though very few of these were large enough to cause symptoms. It must be realized that cartilaginous extensions are fairly common, and that many may produce no symptoms and may only be found at routine autopsy.

Ætiology.—It is perhaps under this aspect that the most recent and interesting work has been done. There are two main theories: the original believes that these lesions are neoplastic in nature, hence they are given the name "chondroma"; according to the more recent theory they are herniations of the nucleus pulposus through the annulus fibrosus with secondary changes in the herniated tissue. As the differentiation has been done from the microscopical examination of these lesions, it is advisable to review briefly the structure of an ordinary chondroma and of the normal nucleus pulposus.

The chondroma [19, 20, 21] is firm in consistency, bluish grey, translucent and usually encapsulated. The microscopic appearance is much like normal cartilage, but does not usually have as regular an arrangement. The matrix has often a definitely fibrillar structure, and the whole tissue may resemble hyaline or fibrocartilage. The nuclei are often in little groups of two to eight cells within a fairly definite capsule, giving the impression of a large multinucleated cell. Fixation and staining often cause them to shrink and assume a vacuolated appearance. In differentiation it may be impossible to separate a chondroma from normal fibrocartilage. Chondromata and the normal nucleus pulposus are easily distinguished, but the differentiation between chondromata and the altered calcified nucleus pulposus is difficult. The large groups of neoplastic cells resemble the notochordal remnants, "the phylasides of Virchow," and unless specific stains, such as that for glycogen, are employed it may be impossible to make an accurate diagnosis.

Most of the earlier writers [4, 6, 7] regarded the tumour as neoplastic, and the tissue removed at operation was certainly compatible with the diagnosis of chondroma. One gets the impression, however, that in many instances this diagnosis was made, not because they were certain it was a chondroma, but because they knew of no alternative diagnosis. The chief points in favour of this view were the microscopical appearance and the long history, suggestive of a benign slowly growing neoplasm. The large multinucleated cells confused some authors, and vague mentions of possible chordoma are found in the early papers. Elsberg [18], in one of his later articles, shows some doubts though he classes them as enchondromata, feeling that they are probably neoplastic but admits the possibility that they are merely due to hypertrophy of the disc. As shown, many of his sections are almost identical with areas of normal disc, but in some there is an increase and change in the cells, but this might be matched from selected areas of normal disc tissue. Alpers, Grant and Yaskin [23] are definitely in favour of this theory, as they feel that the variation in size and immaturity of the cells, with the multinucleated cells and the gradual change of the tissue to normal fibroblasts at its attachment of the disc, indicate a neoplastic process. The gradual onset of symptoms suggests a slowly growing neoplasm, for it is hard to believe that a prolapsed nucleus undergoing changes that solidify it but do not increase its size would, over years, produce signs of compression.

The more recent theory, that of herniation of the nucleus pulposus, was originally proposed by Schmorl [8] and Andrae [9]. They showed that cartilage nodes, single or multiple, are often found in people over the age of 50. These arise under the posterior longitudinal ligament, usually near but not in the midline, and are most frequent in the thoracic and upper lumbar areas, although they have been found in the cervical and lower lumbar regions. They are small, smooth and vary in consistency, and have a definite communication with the nucleus pulposus. Microscopical examination shows a defect in the annulus fibrosus and a prolapse of the nucleus pulposus through this defect. Such a node may resemble the normal nucleus pulposus, or this tissue which has undergone cartilaginous, calcareous or degenerative changes. Peet and Echols [24], Sashin [14], Calvé and Galland [25], Alajounine [26], Petit-Dutailles [28, 29], Mixter and Barr [12], Keyes and Compere [16], and Middleton [2] accept this view.

The mechanism of the production of the node may be considered under the following headings:—

(*a*) The nucleus pulposus is definitely expansile and projects above the cut surface of the disc at autopsy. Keyes and Compere [16] have drilled holes through the annulus fibrosus of animals or cracked it by means of a chisel, and in those which survived for a few weeks necropsy revealed herniation of the nucleus pulposus beneath the longitudinal ligament, producing small nodular swellings.

(*b*) The annulus fibrosus is thinnest and smallest in its posterior portion, and here the disc would be weakest when involved by any diffuse pathological process.

(*c*) The changes in the annulus are produced by trauma in a tissue which has been weakened by degenerative changes. Many of the cases have a history of serious or slight injuries. In support of this is the work of Middleton and Teacher [2] who removed a portion of the spine at autopsy and by means of a press exerted heavy vertical pressure on it. Under this they saw a nodule develop beneath the posterior longitudinal ligament, and later section of the spine showed that the annulus fibrosus had ruptured posteriorly with herniation of the nucleus pulposus.

(*d*) Several facts are in favour of degenerative changes. Alajounine [26] in some of his cases noted thinning of the posterior portion of the annulus with a brownish and degenerated nucleus pulposus. The majority of these cases occur in later life when degenerative changes in other systems are present and recognizable; pure chondromata, on the other hand, are usually found during the adolescent period, and cease growth with the cessation of general growth.

(*e*) Herniation takes place beneath the denticulate posterior longitudinal ligament, and is most pronounced in the weakest areas, namely, lateral to the midline; this explains the usual slightly lateral position of these structures.

(*f*) The structure of the node is that of the normal nucleus pulposus, or of a nucleus pulposus which has undergone degenerative and hyperplastic changes. The structure of pure nucleus pulposus is rare, the usual changes being either the laying down of a dense cartilaginous matrix producing a tissue resembling fibrocartilage, or, in some cases, the occurrence of areas of calcification or ossification producing a firm hard node. To support this many authors lay stress upon the microscopical picture, and particularly on the presence of large notochordal cells. As we have seen previously, similar cells may occur in chondromata; hence the microscopical picture cannot be considered as definitely diagnostic.

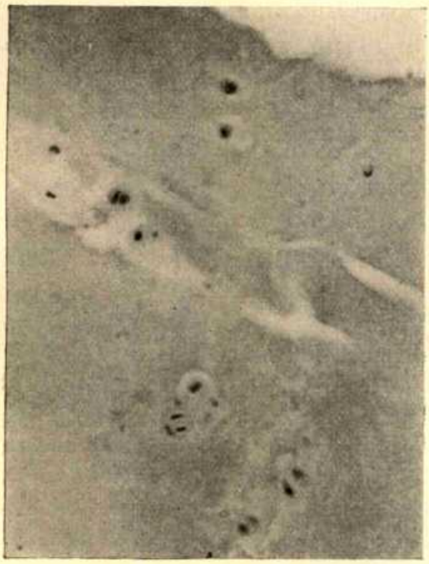

FIG. 1.

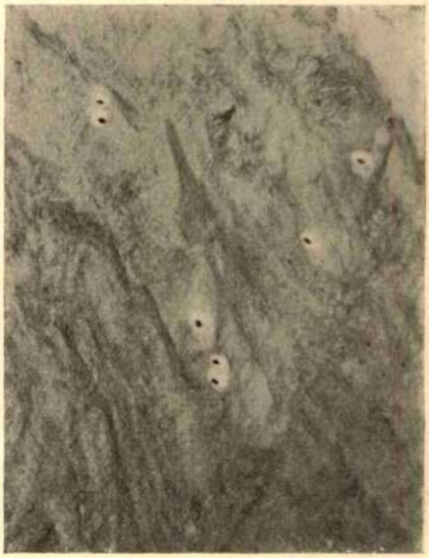

FIG. 2.

FIG. 1.—Section from a portion of the nodule of Case 4, showing a structure very like normal hyaline cartilage.

Fig. 2.—Section from the nodule of Case 5, showing a structure similar to normal fibrocartilage.

In 80 per cent. of my own cases the tissue resembled hyaline or fibrocartilage; in the other two it contained more nuclei with a fair number of groups of cartilage cells, but even these were not cellular when compared to a typical chondroma arising elsewhere in the body. In no case was any tissue resembling the nucleus pulposus or cells of

Virchow found. In general, the structure suggested an origin from the nucleus pulposus with later hyperplasia and fibrocartilaginous changes.

Pathology.—To the naked eye the tumour lies extradurally and beneath the posterior longitudinal ligament, usually slightly lateral to the midline. It is small, 1 to 2 cm. in size, smooth, rounded, often slightly lobulated or oval, and whitish or yellowish white in colour. In consistency it varies from extreme softness to a stony hardness. It is usually encapsulated and in many cases there is a communication between the nucleus pulposus and the tumour.

The microscopical section is varied as the tumour may consist of hyaline cartilage (fig. 1), fibrocartilage (fig. 2), calcified or ossified cartilage, tissue resembling the nucleus pulposus, or tissue consisting of dense fibrous stroma.

CASES.

These cases are all taken from the records of the National Hospital, Queen Square, or were personally observed there in the wards. In all cases but one pathological verification has been obtained.

Case 1.—L. H., female, single, aged 46, was admitted on February 28, 1918, under the care of Dr. James Taylor.

There was no history of any previous injury. In the summer of 1914 she developed sharp shooting pains in the stomach. These soon went away after an abdominal operation, and she remained free from pain from August, 1914, to December, 1916. At this time similar pains, increased by movement of the back, occurred in the right side, and her appendix was then removed. Following the operation the pain slowly disappeared, but returned in June, 1917 and was attributed to post-operative abdominal adhesions. This pain persisted and later became localized in the lumbar region, with a definite radiation to the front of the abdomen. In September, 1917, her legs became weak and stiff, and about this time she fell, fracturing the right leg. During the last month before admission she complained of coldness of her legs and defective control of the sphincters.

General examination revealed only some diffuse non-localized spinal tenderness. The neurological examination revealed normal cranial nerves. There was a slight elevation of the umbilicus when she raised her head and there was a spastic paralysis of her legs, which assumed a position of flexion and adduction and usually showed constant reflex flexor spasms. The sensation to light touch was impaired below the umbilicus and was absent below the first lumbar area. Sensation to pin-prick and to heat and cold was impaired below the umbilicus, and absent below the knees. There was no appreciation of either vibration, position, or deep pressure in the legs. The lower abdominal reflexes were absent, whilst the upper ones were present. The knee and ankle jerks were exaggerated, and the plantar responses were both extensor. There are no available reports of radiography or analysis of the cerebrospinal fluid.

On April 4, 1918, the theca was opened opposite the bodies of thoracic 7 and 8, and a large fusiform cyst of the cord protruded. This burst, discharging a clear fluid. Following this the cord was pulled aside and a hard tumour, the size of a pea, was removed from these vertebræ. This was reported to be cartilaginous tissue with areas of calcification.

Following the operation there was no improvement, and her general condition on discharge was worse than on admission.

Discussion.—There is no doubt that the symptoms were caused by the cyst. However, the earlier symptoms were undoubtedly produced by the cartilaginous node and possibly continuous injury to the cord might have resulted in the cyst. There may be some doubt as to the propriety of including this case amongst the cartilage nodes, but the node had undoubtedly a great deal to do with the course of the illness, and was not merely an incidental finding.

Case 2.—P. W., male, single, aged 25, was admitted on August 9, 1927, under the care of Dr. C. P. Symonds. He had had congenital cataracts. The right eye was removed at the age of 12. The left eye was operated on at 13 years, and since the last operation he had been almost completely blind. There was no history of trauma.

In December, 1926, he complained of pain in the small of his back and in the right hip which increased on bending, and also of slight numbness of the right knee. In January his legs became weak, the numbness increased, and sexual impotence developed. In June the numbness spread to both buttocks and the genitalia. In July the pain decreased as the numbness spread, and he developed loss of sphincter control.

General examination showed an absent right eye; the left eye was blind with corneal opacities and cataracts.

Neurological examination showed normal cranial nerves. Both legs were weak, especially the left which was also wasted. Sensation to light touch was lost over the saddle area and the genitalia. There was hypalgesia over this area, and at the upper level of this there was a burning reaction to pin-prick. The appreciation of vibration was diminished over the left malleolus, but the sense of position was normal throughout. The knee jerks and ankle jerks were absent and the plantar responses were flexor.

Lumbar puncture showed a low pressure and a cerebrospinal fluid which was yellow, coagulated spontaneously and contained 5 mononuclear cells per cubic centimetre. The total protein was 1·5 per cent., the Pandy 2+, and the Wassermann was negative.

Radiography revealed no changes in the spine.

An operation was performed by Mr. Armour on September 8, 1927, when a large outgrowth of the disc was found protruding between the second and third lumbar vertebræ, displacing the cauda equina backwards. As much as possible was removed by chiselling.

The tissue removed was fibrocartilage undergoing calcification. It was not cellular, but contained a few groups of six to eight cartilage cells in different areas.

Following the operation he lost all power in his legs and sphincters, and the hypalgesia increased. These changes, however, began to show improvement on discharge. He improved, and finally in 1928 could stand. However, he injured his back in 1929, and all his symptoms returned. When he was readmitted to the hospital in March, 1930, his condition was much as on the previous admission with the exception of an increased sensory loss. He was again operated upon and some neuro-fibrocartilaginous tissue was removed, but no chondroma found at this time. There was no appreciable improvement on discharge, but since then some improvement has occurred.

Discussion.—This seemed to be a straightforward case until the second operation revealed the presence of a neurofibroma. However, the earlier symptoms were undoubtedly due to the ecchondrosis, which was fairly large.

Case 3.—J. H., male, married, aged 37, was admitted on November 19, 1928, under the care of Dr. G. Riddoch.

In 1926 he fractured his left leg, and following that he complained of some stiffness of the leg. Six months before admission he began to drag his left leg and found that he could not put his heel to the ground because of pain. This pain increased, particularly in the sacral region, and there were also occasional twinges in the left side of his chest. For several months he noticed numbness of both legs, chiefly of the right, and finally, three months before admission, he developed priapismus and a definite difficulty in micturition.

General examination showed some limitation of movement of the mid-thoracic portion of the spine.

Neurological examination.—His legs were spastic, paralysed, and showed numerous flexor spasms. There was weakness of the lower abdominal muscles and of the intercostals below the 8th dorsal. The sensation to cotton-wool was lost below the 7th dorsal area and impaired for two segments above that level. Pin-prick and the sensation to heat and cold were similarly affected, but there appeared to be less change on the right side. There was no appreciation of either vibration or position below the 5th dorsal area. The lower abdominal reflexes were absent, the upper present. The knee-jerks and ankle-jerks were exaggerated and the plantar responses were both extensor. Frequent reflex spasms of the legs occurred, and priapismus was present at times.

Lumbar puncture showed no pressure. The cerebrospinal fluid was yellow and had 8 mononuclear cells per cubic centimetre. The total protein was 0·8 per cent., the Pandy was 3+, and the Wassermann negative. Radiography revealed a small opacity in the vertebral canal opposite the body of the 7th dorsal vertebra.

An operation performed by Mr. Armour on December 4, 1928, revealed a large mass of cartilage arising between the bodies of the 7th and 8th dorsal vertebræ. It compressed the cord from behind and from the left, and was removed.

It consisted of fibrocartilage and included areas which had undergone calcification. After the operation he developed meningitis and died. A post-mortem examination of the cord showed the maximum damage to be about the 9th dorsal segment, but a larger area extending up to the 6th dorsal was definitely necrotic.

Discussion.—The history suggested that the tumour dated back six months only, but its size and calcification indicate it had undoubtedly existed for several years, and possibly might be related to the trauma several years before. The loss of sensation several segments above the node has been observed in several other cases, and might be explained by circulatory damage at a higher level than the node.

Case 4.—H. J., male, married, aged 51, was admitted on August 3, 1930, under the care of Dr. M. Critchley.

In 1926 the patient noted a pain in his lower back described as "lumbago," from which he recovered in three weeks. In March, 1930, he had a severe pain radiating from his hips to his toes. His legs were weak and he could hardly walk. Later he found that the pain was increased by coughing and movements. The weakness increased and he was forced to go to bed. Finally his condition became so bad that he could barely move his legs, particularly the left, in bed. About two months prior to admission he noted numbness of his feet, which gradually spread to the thighs and was associated with the disappearance of the pain. One month before admission he lost control of his bowels and his bladder, finally becoming impotent.

General examination showed no intercurrent disease.

Neurological examination revealed normal cranial nerves. Both legs were very weak, more definitely so the left. The tone was less than normal, and both legs were wasted, the left more so. Fibrillation was not present. Sensation to light touch, pin-prick, heat and cold were lost over both saddle areas, the back of the right thigh, both calves and the outer aspects of each leg. The loss was greater on the right side. The appreciation of both vibration and position in both legs was impaired. The right knee-jerk was normal, the left knee-jerk absent, and both ankle-jerks were exaggerated. A bilateral ankle clonus was present and both plantar responses extensor.

Lumbar puncture revealed a complete spinal block with a clear fluid containing 6 mononuclear cells per cubic centimetre. The total protein was 0·2 per cent., with a Pandy 3+ and the Wassermann reaction negative. Radiography revealed osteoarthritis of the lumbar spine.

An operation by Sir P. Sargent on August 8, 1930, showed a uniform swelling of the conus medullaris.

After the operation the pain was less, but power and sensation were not as good. This condition persisted for several months, at which time he developed pyuria with a marked systemic reaction, finally terminating in his death.

At post mortem no tumour was found in the conus medullaris, but from the disc between 1st and 2nd lumbar a small extradural nodule of firm consistency extended. The cord lay, however, comparatively free. The microscopical examination showed that the nodule was fairly cellular fibrocartilaginous tissue.

Discussion.—This was a nodule producing changes in the conus medullaris. There is a possibility that the "lumbago" four years previously might have been related to this cartilaginous node.

Case 5.—A. L., male, married, aged 44, was admitted on March 5, 1931, under the care of Dr. G. Holmes.

The patient's past history included no evidence of trauma. Five years before admission he noticed some numbness and tingling of the legs and weakness of both lower extremities. At this time he could barely walk, but after three months rest he improved, and was able to resume his work as a shepherd within six months.

There were no further symptoms until March, 1930, when he noticed tingling and numbness of the legs. This spread to the hips and at the same time he became so weak he could not walk. About two months before admission his legs gradually flexed and began to show spasmodic jerkings. For one month he complained of sphincter troubles.

General examination revealed no intercurrent disease.

Neurological examination revealed normal cranial nerves. There was weakness of the lower abdominal muscles and of both legs. The legs were spastic and assumed a position of flexion. Sensation to light touch, pin-prick, heat and cold was impaired below the umbilicus, very poor below the hips, and absent below the knees. Sensation was better on the left side and there was evidence of bilateral sacral sparing, again more marked on the left. The appreciation of both vibration and position were lost in the legs. The upper abdominal reflexes were present while the lower ones were absent. The knee and ankle jerks were exaggerated and the plantar responses were both extensor and associated with a marked withdrawal phenomenon.

Lumbar puncture showed no block, and there was a clear fluid with one mononuclear cell per cubic centimetre. The total protein was 0·09 per cent., with negative Pandy and Wassermann reactions. Radiography revealed generalized osteoarthritis of the spine.

An operation was performed by Sir P. Sargent on April 24, 1931. A firm tumour was found arising from the disc between 9th and 10th dorsal vertebræ, being anterior and extradural in position. This was removed by a gouge. The tissue was reported as fibrocartilage.

After operation he improved for about four weeks but this did not persist and he was sent to a convalescent home. He was readmitted from there in November, 1931, with power absent below the knees and with sensation and sphincter trouble as on the previous admission. He was sent home in February, 1932, and was not heard of again.

Discussion.—This case showed a definite onset five years ago with a complete remission. Because of the trauma of operation and the long duration of the symptoms the improvement was slight.

Case 6.—V. B., male, married, aged 45, was admitted on September 9, 1933, under the care of Dr. J. Collier.

The patient had injured his left cornea at 10 years of age, had fractured both ankles at 23 years of age, and at 25 was in a hospital for pain in the lower back. This required rest for three months and cleared up, but when he was 42 a similar attack occurred requiring two months in bed.

In the summer of 1932 he felt some tingling over the sole of the left foot followed by a similar sensation in, and some weakness of, the fingers of the left hand. During the month before admission he noted that his left foot was numb and cold, that both legs were weak and that finally his right leg became numb. Later the numbness spread to the right lower chest, and just before admission he complained of difficulty in micturition.

General examination revealed a corneal opacity in the left eye.

Neurological examination revealed in the cranial nerves a left pupil which reacted sluggishly to light and fine lateral nystagmus in either direction. There was some weakness and atrophy of the left hand and weakness of the legs, most marked in the dorsiflexors of the left foot. Sensation to light touch was lost on the right foot, while that to pin-prick and heat and cold was absent on the right side below the 5th cervical area. The appreciation of both vibration and position was decreased on the right side. The only reflex changes were bilateral plantar extensor responses.

Lumbar puncture showed a partial block. Cisternal puncture produced a clear fluid with one mononuclear cell per cubic centimetre. The total protein was 0·02 per cent. with a negative Pandy and a negative Wassermann. A later lumbar puncture revealed no block. Radiography showed advanced spondylitis. A lipiodol injection showed some arrest at the level of the 5th cervical vertebra.

An operation was performed by Mr. Taylor on October 3, 1933. The cord was displaced backwards by an extradural mass on the left side arising from the region of the 4th cervical vertebra. It was removed by chiselling. The fibrocartilage presented only a few nuclei.

No change was noted after operation. He was discharged but returned in April, 1934, with more weakness of the left side and a definite right-sided analgesia. After a few months he was again discharged showing a slight improvement. No operation was done at this time.

Discussion.—This was the first case in our series to be verified by lipiodol. It is hard to connect the location of the pain in the early attacks with a node in the cervical region.

Case 7.—L. P., female, married, aged 45, was admitted on July 2, 1934, under the care of Dr. P. Martin.

Seventeen years ago she had her left arm severely crushed in a train wreck. One month before admission she developed a pain in the small of her back. This increased and within two weeks it spread down the right leg and later down both legs. The pain was made worse by walking and coughing, and gradually became so severe that she could not sleep. Three days prior to admission she noticed numbness over the perineum and the backs of both legs. This was soon followed by a loss of sphincter control. There was no definite weakness of the legs.

General examination revealed the amputation of her left arm and an area of tenderness over the sacral vertebræ.

Neurological examination revealed normal cranial nerves. There was some weakness in the glutei and hamstrings of the right leg. There was complete loss of all forms of sensation over the saddle area and the backs of her legs. Both ankle-jerks were lost and the plantar responses were flexor.

Lumbar puncture revealed no block. The fluid was clear with one mononuclear cell per cubic centimetre. The total protein was 0·075 per cent., the Pandy was weakly positive, and the Wassermann negative. Radiography revealed a normal spine. An injection of lipiodol showed arrest at the lower border of the fourth lumbar vertebra.

An operation by Mr. Taylor on August 14, 1934, showed some bulging of the anterior thecal wall and a smooth yellow mass arising from the disc between 4th and 5th lumbar areas. This was removed by dissection and curettage. This tissue was reported as fibrocartilage with few nuclei.

She had a very good post-operative recovery and on discharge was walking well. The ankle-jerks were returning and there was little evidence of sensory loss.

Discussion.—The short history and easy removal produced good results. There was probably no relation between the trauma seventeen years previous and the node.

Case 8.—A. C., female, married; aged 43, was admitted on June 16, 1935, under Dr. G. Holmes.

Seven years ago she complained of "lumbago," which consisted of pain in the small of her back. This recurred five years ago and at this time the pain spread down the right leg. There was no history of trauma to be obtained.

When the pain ceased five years ago the right foot remained numb and this persisted until admission. There was no further pain until January, 1934, when it returned in the same area as previously. About this time she fell and injured her back. The pain became much worse and numbness developed in the soles of both feet spreading to the knees in September, and to the hips in November. In these latter months she noted weakness of the legs and loss of sphincter control with incontinence.

General examination revealed some tenderness over the sacral vertebræ.

Neurological examination revealed a slight bilateral weakness of the flexors of the hip and adductors of the thighs. Sensation to light touch was normal, but that to pin-prick and heat and cold was decreased between the 10th thoracic and 1st lumbar areas, definitely impaired over the 2nd and 3rd lumbar areas, and slightly on the lower lumbar areas, but intact in the areas of the sacral roots. The appreciation of both vibration and position was absent in both legs. The knee-jerks and ankle-jerks were exaggerated with ankle clonus and bilateral plantar extensor responses.

Lumbar puncture revealed no block. The fluid was clear with no cells and a total protein of 0·1 per cent. The Pandy was 1+ and the Wassermann negative. Radiography revealed osteoarthritis of the lower lumbar spine.

An operation was performed by Mr. Taylor on March 26, 1935. The dura was pushed forward by an intensely hard osteochondroma arising between 1st and 2nd lumbar vertebræ, probably from the disc. Removal was impossible.

After the operation she showed a marked paralysis of both legs and a fairly complete sensory loss below the first lumbar area and a slight sensory loss below the 10th thoracic. At the time of writing some recovery had occurred in both power and sensation.

Discussion.—This case had a very long history dating back seven years with a definite remission. The trauma of operation produced a damage to the cord with an increase of all symptoms. In spite of the lack of a pathological report, the clinical history and operative findings appear diagnostic enough to include this in our present series.

Case 9.—J. K., male, married, aged 59, was admitted on July 6, 1935, under the care of Dr. S. A. K. Wilson.

There was no history of trauma, but about five years before admission he noticed a severe pain in the right calf. This spread to involve the whole of his back and the outer side of the right leg. He was placed in a cast for several months with good results, although the pain tended to return at different times with exercise. In the early part of 1935 he noticed numbness beginning in the right buttock, which spread first to the right foot and then to the left buttock and left foot, and finally to the genitalia. With the numbness pain tended to disappear. A few months later he began to lose control of his sphincters. The sole motor symptoms were only a slight stiffness and weakness of the right leg.

General examination revealed a definite rigidity of the lumbar spine.

Neurological examination showed that the cranial nerves were normal. There was, a definite weakness and atrophy in the right leg, and a slight weakness of the left leg. Sensation to light touch, pin-prick, heat and cold was slightly impaired from the 1st to the 4th lumbar areas, and lost below this level. The appreciation of vibration was lost in the right malleolus, while the sense of position was normal throughout. The ankle-jerks were absent and the anal reflexes very poor. Very little plantar response could be obtained.

Lumbar puncture revealed no block. There was a clear fluid with no cells. The total protein was 0·11 per cent., the Pandy 1+ and the Wassermann negative. Radiography revealed marked spondylitis, and a lipiodol injection was arrested at the level of 4th lumbar vertebra.

An operation was performed by Mr. Jackson on April 9, 1935. The cauda equina was displaced backwards by an extradural mass arising from the region of 4th lumbar vertebra. This was enucleated. The tissue was fibrocartilage with few nuclei and no evidence of calcification.

He improved after the operation and was discharged with a fair return of sensation and good sphincter control, but no change in power.

Discussion.—A typical cauda equina syndrome with a definite five year history.

Case 10.—K. S., female, married, aged 59, was admitted on March 21, 1935, under Dr. G. Holmes.

There was no history of trauma. Ten years prior to admission she noticed that her legs would give out while walking. This increased and the right leg began to drag. One year later she developed severe pain in her right chest, paroxysmal and irregular. This pain shifted and gradually went to the right leg, which at the same time became definitely weaker.

These pains in the right leg persisted with definite exacerbations and became gradually more severe. On admission she was subject to very sharp sudden spasms of pain which were severe enough to make her cry out. There was no definite cause for these and they occurred with a marked periodicity, every two to five minutes, and lasted about one-half to one minute. They tended to remain in the same area, namely, the front of the right leg from the hip to the toes. During the last five years the right leg became much weaker, and during the last six months definite weakness developed in the left leg. Before admission she was bedridden with a marked loss of sphincter control and incontinence.

General examination revealed tenderness of the spine between the 3rd and 5th dorsal vertebræ.

Neurological examination revealed definite weakness of the recti abdominis and the intercostals below the 7th dorsal. There was no power in the right leg and very little in the left. Both legs were in the position of spastic extension. Sensation to light touch was decreased below the 6th dorsal area. There was hyperæsthesia on the 2nd dorsal, slight hypalgesia on the 5th to 7th dorsal areas and almost complete loss below this level. There was some bilateral sacral sparing, more marked on the right side. The appreciation of both vibration and position was very poor in both legs, more so the left. The upper abdominal reflexes were present, the lower ones absent, the knee-jerks and ankle-jerks were exaggerated and the plantar responses were extensor. There was a bilateral ankle clonus and a marked flexor withdrawal response of both legs.

Lumbar puncture revealed a partial block. The fluid was clear with no cells and a total protein of 0·3 per cent. Pandy was 2+ and the Wassermann reaction negative. Radiography revealed an area of calcification in the spinal canal at the level of the disc between the 6th and 7th dorsal vertebræ and some erosion of the margins of the intervertebral disc.

An operation was performed by Mr. Taylor on April 5, 1935. The cord was displaced by an anteriorly placed extradural mass attached to the disc between the 6th and 7th dorsal vertebræ. It was calcified and lay more on the right side. It was the size of a cherry and was removed by chiselling.

The tissue was reported as normal bone and fibrocartilage with extensive calcification. Its general appearance was like normal disc tissue.

After the operation she had still complete paraplegia with anæsthesia below the 6th dorsal and lost sphincter control. When last seen there was slight improvement in power and sensation.

Discussion.—An unusual feature was the peculiar rhythmical pain which occurred with no apparent cause. It was a very long history, at least ten years, with definite remissions. There was also a peculiar but definite level of hyperæsthesia several segments above the node.

ANALYSIS OF CASES.

This analysis is based upon the following fifty-eight cases: Six reported in detail by Elsberg [18], seven by Stookey [7], six by Steinke [17], nineteen by Mixter and Barr [12], two each by Peet and Echols [24], Robineau [30], and Dandy [31], one each by Crouzon, Petit-Dutailles et Christophe [32], Alajounine et Petit-Dutailles [26], Bucy [33], and Alpers, Grant and Yaskin [23]. To these were added the ten cases from the National Hospital, Queen Square.

Age.—The average age was 45 years with a variation from 20 to 63 years.

Sex.—Roughly, two-thirds were males.

Trauma.—Definite evidence of trauma could be obtained in about one-third of the cases, varying from a fractured leg to a severe blow in the back.

Initial symptoms.—These may be divided into the prodromal symptoms which cleared up, and the initial symptoms proper with which the illness began. The prodromal symptoms were described as lumbago, sciatica, or as pains in the back, and as they preceded the symptoms of the spinal disease and corresponded in location to these symptoms, it is probable they were related. Roughly speaking, about one-half of the cases had such symptoms, and the average duration of these was five years though they varied from two to ten years. About 90 per cent. of these prodromal symptoms were sensory complaints, usually pain, the rest some form of paræsthesia. In almost all cases the initial symptoms proper were sensory, chiefly pain in the back, but some first complained of weakness or stiffness of the legs. The average duration of these symptoms was eighteen months, varying from one month to seven years.

Course of the disease.—The initial symptom, almost always pain, was followed by motor disturbances and in the end by disorders of the sphincters. The interval between the onset of the sensory and the appearance of the motor symptoms averaged about twelve months, and that between the motor disturbances and the lack of sphincter control was ten months. The usual history was an onset with sensory symptoms, then about half way through the illness motor disturbances appeared, and finally only a few months before admission sphincter troubles became apparent. In the rarer cases which began with motor symptoms, sensory disturbances occurred next and sphincter palsies developed last. The earliest sensory symptom was most commonly pain, followed by numbness or rarely by other paræsthesiæ. When numbness ensued the pain usually disappeared, but in a few cases where the numbness was referred to a lower level than the pain both persisted. These pains were often referred to the distribution of the root compressed and as such were a good indication of the level of the lesion. In most cases the pains were increased by movement, coughing, or straining and eased by rest. The paræsthesiæ were generally described as tingling, "pins and needles," or, rarely, by peculiar sensations of cold.

The motor disturbances commonly began as stiffness or weakness of the legs, but in a few the arms were first affected. In almost every case motor symptoms developed with the exception of a few cases where the lesion lay in the lower lumbar region.

Sphincter disturbances were observed in about two-thirds of the cases; it generally commenced as hesitancy of micturition and constipation and proceeded to incontinence and loss of sensation of these acts. In a small number of cases impotence or some sexual disturbance was recorded.

Examination of the patient.—It is an interesting fact that practically no evidence of intercurrent disease was reported. The motor signs depend upon the location of the node. In all the cases except a few in which the cauda equina was involved some evidence of disorder of the motor system could be found. No atrophy of muscles or fibrillation was observed in the series at the National Hospital except in a few cases where the cauda equina was involved. This is surprising as the node lying ventral to the spinal canal must first have compressed the motor roots. In a few cases, however, particularly those of Stookey [7], definite atrophy and fibrillation were reported.

In addition to the subjective symptoms which have already been discussed objective sensory changes are present in over 90 per cent. of all cases. In those in which the sensation escaped the lesions involved only the cauda equina. In most cases the changes were a definite loss to painful stimuli, to light touch, to the perception of vibration and of the sense of position. In a small number of cases the loss to light touch was much less than the loss to painful stimuli. In very few of the cases was there a sparing of sensation on the sacral areas. In none of the cases at the National Hospital, and in a few only of the total series, were those forms of sensation conducted by the posterior columns of the cord unaffected. This is surprising as from their position it might be expected that these lesions would affect the anterior columns of the cord more severely than the posterior columns. Sensory changes were present at a higher level than the node in several of our cases, in three at least two segmental areas above that corresponding to the lesion. It must be therefore assumed that there were some changes in the cord or roots above the node; these were probably secondary to circulatory disturbances. Three similar cases have been recorded, two by Elsberg [18] and one by Robineau [30], with sensory changes two segments above the level of the nodes.

It is interesting that sensory and motor disturbances were present in every case in which the lesion lay above the lower lumbar region, and that they were absent only in some where the cauda equina alone was involved.

In about half of the cases some tenderness of the vertebræ, or limitation of movement of the spine, could be demonstrated.

Reflexes.—There is nothing specific in the state of the reflexes, they are similar to those obtained in other forms of spinal compression. In cases described by Mixter and Barr [12] in which the cauda equina was compressed the ankle-jerks were absent although there was no definite motor or sensory disturbance.

Cerebrospinal fluid.—In about 25 per cent. of the reported cases there was a complete block, and in about 50 per cent. a partial block. The protein was markedly increased in 40 per cent. of the cases, moderately increased in another 40 per cent. and normal in the rest. In practically all cases the cell count was below 10 per cubic millimetre and the cells were all mononuclears. In no case was the Wassermann reaction positive.

Radiography.—The vertebræ showed no specific changes, but in a few cases osteoarthritis was observed. In seven cases changes could be observed in the intervertebral discs, either calcification of its centre or irregular narrowing of the disc itself. It is probable that such changes could be more frequently seen if attention were specifically directed to them. In two of the National Hospital cases the nodes were calcified and visible, but this has not been reported in any other case. In about 40 per cent. of the cases the fall of lipiodol was arrested at the site of the lesion, and by that technique the level of the node was confirmed.

Location of the nodes, as proven by operation in the National Hospital series, was as follows: 1 case was in the cervical region, 4 were in the thoracic region, and 5 in the lumbar region. When all the cases reported are considered about 17 nodes were in the cervical region, 13 nodes in the thoracic region, 27 in the lumbar region, and 1 in the sacral region. The nodes tend to be more common in certain regions as 10 were found between the 4th and 5th cervical vertebræ, 7 between the 6th and 7th thoracic vertebræ, and 21 between the 3rd and 5th lumbar vertebræ.

Differential Diagnosis.

The symptoms and physical signs are essentially those of spinal compression. The following points are in favour of a cartilage node: a history of trauma preceding the illness; intermittent root pains present for a long period of time, even four to five years, before the onset of spinal symptoms; an initial onset of root pain followed by weakness and later by sphincter troubles. Neither the motor nor the sensory signs are characteristic. The spinal fluid shows no characteristic changes, but radiography may reveal the presence of an altered intervertebral disc or calcification of the node. It is probable that as radiologists pay more attention to the structure of the intervertebral disc earlier diagnosis may be possible.

Prognosis.

An analysis of the cases comprising the whole series throws some light upon the factors which determine the prognosis. On the whole age and sex are of little significance. It might be expected that the prognosis would be more favourable in younger patients, but patients as old as 61 have made complete recovery. The level of the node is more important, as patients with nodes in the cervical region do fairly well after its removal, those in whom the thoracic segments are involved do very poorly, and the prognosis is most favourable when the node lies in the lumbar region, indeed very few of the latter fail to improve after successful operation. The shorter the duration of the symptoms the better the prognosis. Patients with symptoms other than of pain lasting over one year do not do well, but the occurrence of pain and no other sensory symptoms for years does not preclude considerable improvement after operation. One patient who had pain for five years prior to operation made a good recovery. Weakness and stiffness lasting over a year are signs of a poor outlook.

The consistency of the tumour is important. When the node is calcified or ossified the improvement after the operation has usually been slight, certainly much less than when the tumour removed was soft. The trauma of a severe operation seems to increase the symptoms and may produce an almost complete transverse lesion of the cord. Currettage or dissection produces far better results than chiselling or gouging.

In the National Hospital cases the following figures were obtained: 20 per cent. showed definite improvement, 10 per cent. slight improvement, 20 per cent. no change, and 50 per cent. became worse after the operation. In the total series the prognosis was much better as about 70 per cent. improved, 5 per cent. were unchanged, and only 20 per cent. were worse after the operation. The factors given above explain the discrepancy in the figures.

CONCLUSIONS.

(1) Ten cases of spinal compression due to ecchondrosis of the intervertebral disc are reported, and the total of fifty cases collected from the literature have been analysed.

(2) The ætiology of the condition has been discussed; the tumour is probably due to a herniation of the nucleus pulposus through the annulus fibrosis.

(3) The cases have been analysed in the hope of obtaining a characteristic clinical picture, but although this has not been possible a number of suggestive diagnostic features have been indicated.

I wish to express my thanks to the Medical and Surgical Staff of the National Hospital for permission to use the clinical and pathological material on which this communication is based, and to Dr. Greenfield for his help in studying the pathological material.

BIBLIOGRAPHY.

[1] Oppenheim. "Text Book of Nervous Diseases," vol. i, 1911.
[2] Middleton, G. S., and Teacher, J. H. *Glasgow Med. Journ.*, 1911, **76**, 139.
[3] Goldthwaite, J. E. *Boston Med. and Surg. Journ.*, 1911, **164**, 365.
[4] Potel, G., and Veaudeau. *Rev. Chir.*, 1913, **47**, 713, and **48**, 477.
[5] Delaginière. *Thèse de Paris*, 1928.
[6] Elsberg. "Tumours of the Spinal Cord," 1925.
[7] Stookey, B. *Arch. Neur. and Psych.*, 1928, **20**, 275.
[8] Schmorl, G. *Fort. Geb. Rönt.*, 1929, **40**, 629.
[9] Andrae, R. *Beit. Path. Anat. Allg. Path.*, 1929, **82**, 464.
[10] "Gray's Anatomy," ed. 25, 1932.
[11] Sharpey-Schafer. "Essentials of Histology," ed. 13, 1934.
[12] Mixter, W. J., and Barr, J. S. *New Eng. Med. Journ.*, 1934, **211**, 210.
[13] Mooney, A. C. *Brit. Journ. Radiol.*, 1934, **7**, 46.
[14] Sashin, D. *Arch. Surg.*, 1931, **22**, 527.
[15] Geist, E. S. *Journ. Amer. Med. Assoc* , 1931, **96**, 1676.
[16] Keyes, D. C., and Compere, E. L. *Journ. Bone and Joint Surg.*, 1932, **14**, 897.
[17] Steinke, C. R. *Journ. Nerv. and Ment. Dis.*, 1918, **47**, 418.
[18] Elsberg, C. A. *Bull. Neur. Instit.*, 1931, **1**, 350.
[19] Boyd. "Surgical Pathology," ed. 3, 1933.
[20] MacCallum. "Text Book of Pathology," ed. 5.
[21] Delafield and Prudden. "Test Book of Pathology," ed. 15, 1931.
[22] Bailey. "Intracranial Tumours," 1933.
[23] Alpers, B. J., Grant, F. C., and Yaskin, J. C. *Annals Surg.*, 1933, **97**, 10.
[24] Peet, M. M., and Echols, P. H. *Arch. Neur. and Psych.*, 1934, **32**, 924.
[25] Calvé, J., and Galland, M. *La Presse Méd.*, 1930, **38**, 520.
[26] Alajounine, T., and Petit-Dutailles, D. *Ibid.*, 1930, **38**, 1657 and 1749.
[27] *Idem.* *Bul. and Mem. Soc. Nat. Chir.*, 1928, **54**, 1452.
[28] Petit-Dutailles, D., and Lereboullet, J. *Ibid.*, 1934, **60**, 691.
[29] Petit-Dutailles, D. *Rev. Méd. Franc.*, 1934, **15**, 275.
[30] Robineau. *Bul. and Mem. Soc. Nat. Chir.*, 1929, **55**, 937.
[31] Dandy, W. E *Arch. Surg.*, 1929, **19**, 660.
[32] Crouzon, O., Petit-Dutailles, D., and Christophe, J. *Rev. Neur.*, 1931, **38**, 612.
[33] Bucy, P. C. *Journ. Amer. Med. Assoc.*, 1930, **94**, 1552.

The following are included for reference:—

[34] Cadwallader. "Diseases of the Spinal Cord," 1932.
[35] Adson, A. W. *Northwest Med.*, 1925, **24**, 309.
[36] Von Pechy, K. *Frank. Zeitschr. Path.*, 1929, **37**, 562.
[37] Veraguth, O. *Schweitzer. med. Woch.*, 1929, **59**, 154.
[38] Adson, A. W., and Ott. *Arch. Neur. and Psych.*, 1922, **8**, 520.
[39] Elsberg, C. A. *Ibid.*, 1922, **8**, 502.
[40] *Idem.* *Ibid.*, 1929, **22**, 949.
[41] *Idem.* *Surg. Gyn. and Obstet.*, 1928, **46**, 1.
[42] Schmorl, G. *Verhand. Deut. Orthopad. Gesell.*, 1926, **21**, 3.
[43] Grant, F. C. *Amer. Journ Surg.*, 1934, **23**, 89.
[44] Mauric, G. "Monograph on the Intervertebral Disk," 1933.
[45] Calvé, J., and Galland, M. *Journ. Bone and Joint Surg.*, 1930, **12**, 555.
[46] Ballif, L., Moruzi, A., and Ferdman, M. Vol. Jubilaire de C. I. Parhon, Jassy, 1934-18.

PROGRESSIVE DEMENTIA, WITHOUT HEADACHE OR CHANGES IN THE OPTIC DISCS, DUE TO TUMOURS OF THE THIRD VENTRICLE.

BY GEORGE RIDDOCH, M.D.

IN the presentation of two cases of tumour of the third ventricle attention will be drawn less to focal symptomatology than to the occurrence of progressive dementia in the absence of severe headache, vomiting, and of either papillœdema or optic atrophy. As will be seen, gross hydrocephalus was present in both cases and was, I believe, the cause of the mental deterioration. A complete dissociation of this kind is not common with intracranial tumours in any situation when the illness has lasted for a considerable time, and all the more with tumours which are so placed as to obstruct the circulation of the cerebrospinal fluid.

Tumours in the third ventricle are characterized, sooner or later, by manifestations of severe hydrocephalus which may be paroxysmal or continuous, depending upon whether the obstruction of the cerebrospinal fluid pathway is intermittent or not. For example, with colloid cysts, especially when anteriorly placed, as in Case 1, paroxysmal attacks of hydrocephalus are common and can sometimes be arrested by altering the position of the head—(Weisenburg [4], Dandy [1], Fulton and Bailey [2]). Since these tumours are benign and slow growing, long intervals may separate the attacks until the blockage of the foramina of Monro, or of the Sylvian aqueduct, becomes complete. On the other hand, when the tumour is posterior and is not pendulous, progressive hydrocephalus develops from either plugging of the aqueduct or compression of it from invasion by the neoplasm of the mid-brain. This result is illustrated by Case 2.

Most of the symptoms and signs of hydrocephalus—severe headaches, vomiting, papillœdema, weakness, unsteadiness, and mental dullness—are usually present in varying intensity and often usher in and remain the prominent features of the illness. If the attacks of hypertension are relatively short, papillœdema may be absent until some permanent obstruction occurs; or instead of swelling of the optic discs, primary optic atrophy with visual field defects, sometimes bitemporal, may result from pressure on the optic tracts or chiasma by the floor of the distended third ventricle. But the slow development of dementia without headache, vomiting, or alteration in the optic discs or visual fields, as in the cases about to be described, is exceptional.

Case 1.—H. N., male, aged 66. Single. According to his relatives he had always been a dull fellow and had retained his job as a Stockbroker's clerk in his brother's office because of their relationship. His work had never been quite satisfactory. His general health had, however, been good until twelve years ago when having tea in a tea-shop he was seen to fall to the ground and was taken unconscious to Middlesex Hospital. He remained in coma for fourteen hours. Sugar was found in his urine, but it disappeared and, since consciousness spontaneously returned, he was discharged under the diagnosis of an unexplained cerebral attack. On inquiry, his sister said that he had complained of headaches before the attack, but was not known to have had any since then.

He remained well until two or three years ago when he became lethargic, so that he was apt to go to sleep at any time, and he became still more inefficient in his work than he was before. The sleepiness and dullness varied but tended to increase. His brother, who was his employer, found that he was slow, forgetful and inclined to repeat himself. In fact, as was said, he behaved like an old man. He complained of a continual sense of fatigue.

On March 20, 1934, he was admitted to the London Hospital. A week before, he was found unconscious on the pavement with a cut across his left eyebrow and his left eyelids were swollen and blue. He soon partly regained consciousness but since then, until his death on April 11, 1934, he remained dull, sleepy and incontinent. His mental condition varied, but as a rule he could be roused to answer questions and to co-operate in an examination. But his answers, although apparently correct, were slow and he was obviously disinterested in everything that happened to him and around him. He did not make any complaint and denied having headache. His memory was very poor and unreliable for recent and past events and he was quite apathetic. Sometimes he was awake during the day for long periods, but at other times he remained asleep so long as he was left alone. He had an excellent appetite and ate enormously, but had to be fed.

On examination, he was thin and looked older than his age. He had not, however, lost weight. His peripheral arteries were firm and tortuous and his retinal arteries narrow. His heart sounds were feeble and his blood-pressure readings 110/75. His pulse-rate was between 50 and 60 and his temperature subnormal. His urine, blood sugar and blood urea were normal. There was no polyuria or polydipsia. Speech and articulation were normal except that he spoke slowly. It was impossible to chart his visual fields by perimeter, but they were full to confrontation tests. His optic discs were clear and there were no hæmorrhages nor exudates in his retinæ. His ocular movements were full, and diplopia, squint, nystagmus and paralytic ptosis were absent.

His pupils were central and equal but small and irregular in outline, and failed to react to light. The reaction on convergence was poor, perhaps partly from insufficient effort on his part. There was slight left lower facial weakness. The functions of the other cranial nerves were normal.

All voluntary movements of his limbs were feeble and shaky, but there was no dystonia or gross ataxia. He occasionally showed a grasp reflex with his right hand. He was confined to bed and was too feeble to sit up without support.

The tendon-jerks of his upper and lower limbs were present and equal on the two sides but were diminished; his abdominal reflexes were present and equal and his plantar responses were extensor.

Sensory testing was unsatisfactory, but there was no apparent gross loss to light touch, pin-prick, passive movement and postural change.

X-ray examination of his skull was negative.

On admission, he was ordered daily rectal injections of three ounces of magnesium sulphate in six ounces of water and a few days later was lumbar punctured. The cerebrospinal fluid pressure, with the patient in the horizontal position, was found to be 160 mm. of water. (This comparatively low reading in view of the severe hydrocephalus will be discussed later). The fluid contained 0·5 per cent. of protein but did not present any other abnormality.

Although tumour of the third ventricle was suspected, the differential diagnosis from traumatic cerebral lesions in an arteriosclerotic subject was difficult and three weeks after admission Mr. Cairns tapped the occipital horn of both lateral ventricles, and obtained fluid at a depth about 4 cm. from the dura. The pressure was surprisingly subnormal. The fluid contained less than 10 mgm. of protein per 100 c.c. 60 c.c. of air was injected into each ventricle and the ventriculograms showed enormous and symmetrical distension of the lateral ventricles with air in the third ventricle. The foramina of Monro could be seen to be enlarged and the curved anterior end of a tumour in the third ventricle was clearly defined.

Operation for removal of the tumour by opening one lateral ventricle and incising the foramen of Monro was considered but was not attempted on account of the patient's condition. He died two days later.

Throughout the course of his illness his condition varied, but he gradually became worse mentally and physically. Nevertheless, headache, vomiting and alteration in his optic discs remained absent.

An autopsy was carried out on the day after death. There was an enormous distension of the lateral ventricles with thinning of the brain substance and flattening of the convolutions. The third ventricle was also greatly enlarged, especially antero-posteriorly. A round colloid cyst measuring over 2 cm. in diameter was attached to the choroid plexus. It lay behind the foramina of Monro, which were grossly enlarged, and well in front of the aqueduct of Sylvius which was narrowed. It bulged into the lateral ventricles from which it was separated by the roof of the third ventricle. The quadrigeminal plate was flattened and above it were the greatly enlarged posterior parts of the lateral ventricles.

Comments.—In spite of gross hydrocephalus of the lateral and third ventricles there was no thinning of the skull or abnormal convolutional markings. The clinical picture was one of slowly progressive dementia with lethargy of at least twelve years' duration, which varied in severity from time to time but without an acute episode until he had his second attack of unconsciousness. All this indicates that the main explanation of the absence of headache, vomiting and papillœdema lies in the very gradual and intermittent evolution of obstruction to the cerebrospinal fluid circulation. The absence of increased pressure in the ventricles and on lumbar puncture supports this view, although the therapeutic dehydration by hypertonic solutions of magnesium sulphate may have played a part.

The first attack of unconsciousness, which was preceded by headache twelve years ago was presumbly due to acute obstruction, but the cerebrospinal fluid circulation became, after a short time, re-established.

The fact that, according to his relatives, he had always been a dull person, raises the question whether the pathological process dates back longer than the history would at first seem to indicate.

It will be noticed that in this case the abnormal sleepiness is attributed, like the dementia, to general cerebral compression and not to focal disturbance of hypothalamic neural mechanism. I agree with Fulton and Bailey [2] that hypersomnia to have definite localizing value should precede the onset of mental dulness.

Finally, the cause of the hydrocephalus is interesting. Since the third ventricle was undoubtedly greatly enlarged, there must have been obstruction of the aqueduct of Sylvius which could not, however, have been directly due to the tumour when its position is considered. At autopsy, the aqueduct was found to be flattened from above downwards and the quadrigeminal plate compressed due, almost certainly, to the overlying distended posterior parts of the lateral ventricles. This then was the cause of the hydrocephalus of the third ventricle as well as of the pupillary abnormalities, namely smallness, irregularity and reflex iridoplegia.

The mechanism by which the tumour produced hydrocephalus of the lateral ventricles has still to be explained. Its size alone may have impeded the flow of fluid through the third ventricle, but it is likely also that it caused intermittent obstruction of the foramina of Munro at least at a stage in its growth when it was perhaps pendulous, or at any rate more movable than it was at a later stage. If this explanation is valid then the increased size of the foramina has been compensatory.

Case 2.—S. C., male, aged 55. On the whole he had been a healthy man until the onset of the illness about to be described.

Throughout his life he had been remarkably free from headaches, but had been subject to occasional "rheumatic" pains in different parts of his body.

In the early part of the summer, 1933, after a period of hard public work, he complained of feeling tired and of being a little unsteady on his legs. He recognized that his memory was failing and that he was unusually sleepy. In August he went to Wiesbaden, as he had done before, with his wife who wished to undergo treatment. Whilst there, because of slight pain and stiffness in the upper part of the back of his neck, he was persuaded to have a course of baths. This made him still more tired and unsteady and by the time he returned to London in September, 1933, he had become considerably worse. He was more dull, sleepy and feeble. He had lost interest and initiative and his memory was so poor that he continually misplaced things and forgot what he wanted. He was aware of these deficiencies, was worried about them and was afraid that he was going to die.

According to his wife he was different from his usually alert self and was at times confused and had obvious difficulty in thinking.

He became fairly rapidly worse during the two days before I saw him with his doctor on September 30 and had been incontinent. It was found that he had been sweating profusely and continued to do so until he died. In addition there was slight fever for no obvious cause. His weight had not varied much and he had not been abnormally thirsty. He did not think that there was anything wrong with him or that he had been ill. He believed that his memory was excellent and his mind clear, in fact, he seemed to be surprised that he was being kept in bed and that a fuss was being made about him. He denied having headache or any other symptom.

He was in a happy, fatuous mood and laughed in rather a silly way. His memory defect was gross and his power of attention and co-operation poor. He was disorientated but not deluded, except about his own condition. He was a florid, well-nourished man. His heart, arteries and blood-pressure were normal for his age. Articulation was slow and tremulous, but speech was normal. Sensory testing was, because of his mental condition, not very reliable, but to rough tests his visual fields appeared to be full. His optic discs were clear and retinal arteries good. His pupils were moderately dilated, the right being larger than the left, both were irregular and reacted very poorly to light, especially the left, but well on convergence. His ocular movements were full and there was no nystagmus, squint or ptosis. When he spoke there was twitching of his face and his tongue was tremulous, but the functions of his cranial nerves were otherwise normal.

There were general weakness, slowness and gross tremor of his limbs on voluntary movement, but no dystonia or ataxia. The tendon-jerks of his upper and lower limbs and abdominal reflexes were present and equal on the two sides, and both plantar responses were flexor. There did not appear to be gross defect in sensibility to light touch, pin-prick and passive movement and change in position.

A provisional diagnosis of dementia paralytica was made, but the Wassermann reaction was found to be negative in blood and cerebrospinal fluid. On lumbar puncture the cerebrospinal fluid pressure, with the patient horizontal, was over 300 mm. of water and the only abnormalities found in the composition of the fluid were a protein content of 0·075 per cent. and weakly positive globulin reactions.

Four days later slight weakness of the lower part of his face and of his upper limb as well as an extensor plantar response on the right side were found.

On these findings a ventricular tumour was suspected. X-ray examination of the skull showed increased convolutional markings and indistinctness of the posterior clinoid processes. On ventricular puncture the pressure was 110 and the protein content 0·005 per cent. was normal. Ventriculograms demonstrated marked dilatation of the lateral ventricles and the anterior part of the third ventricle.

In retrospect it ought to have been clear that the tumour lay in the third ventricle, but the posterior fossa was explored on October 6 with negative results.

The patient died on the following day.

At autopsy the cerebral convolutions were found to be flattened. Both lateral ventricles were greatly dilated. The third ventricle was also enlarged and in its posterior part there was a tumour which measured 3·5 cm. from before backwards and 2 cm. from above downwards. It extended forward to the level of the foramina of Monro, which were much larger than normal, being 1 cm. by 0·4 cm. Above, the tumour was not attached to the tela choroidea and the anterior pillar of the fornix. Behind it extended into the aqueduct of Sylvius for a distance of 0·6 cm. reaching the level of the junction between the superior and inferior colliculi. Below this part of the tumour was the slightly flattened cerebral peduncles. The antero-inferior border was free. Laterally, the tumour extended into the inner part of each optic thalamus for a short distance. The internal capsules were compressed.

Histologically it was found to be a spongioblastoma multiforme.

Comments.—In this case the clinical picture of progressive dementia, dysarthria, weakness, tremor and reflex iridoplegia without headache or papillœdema, closely resembled that of dementia paralytica running a fairly rapid course, until the blood and cerebrospinal fluid were examined. The key to the correct diagnosis of tumour was the raised cerebrospinal fluid pressure on lumbar puncture.

In the localization of the tumour we were unjustifiably led astray by the evidence of air in the third ventricle in the ventriculograms. Ventriculography has been shown by Dandy to be an aid of great importance in the diagnosis of third ventricle tumours, but to be of any value the X-ray appearances must be correctly interpreted and the radiographic technique of high standard. Unfortunately, in this case, the films did not show clearly enough that air was present only in the anterior part of the third ventricle.

The emotionalism which was associated with dementia in this case, but not in Case 1, is of interest and was probably due to invasion of the optic thalami by the tumour. Nevertheless, emotional facility when inhibition is reduced, as it is in dementia, is often an exaggerated expression of the natural reaction of the individual. S. C. (Case 2) was by nature a cheerful person, whilst H. N. (Case 1) was dull and apathetic and became more so throughout his illness.

CONCLUSIONS.

These cases illustrate the fundamental importance in clinical neurology of the time-factor which determines the presence or absence of many symptoms and bears so much on the evolution of illness.

Contrast the abolition of function below the level of an acute, severe spinal lesion with the slowly developing disturbance of function associated with gradual spinal compression. No better examples could be given of the influence of the time-factor in the development of symptoms than headache and papillœdema in intercranial hypertension. When pressure within the skull is rapidly raised, as from sub-arachnoid arterial hæmorrhage, headache is an almost immediate complaint, before consciousness is lost, and papillœdema, often with hæmorrhages, develops within a short time. On the other hand, slowly increasing pressure from tumour, whether local or general, may for long be unassociated with either of these symptoms. In comparison with the development of focal manifestations, their not infrequent late appearance with meningiomas and slow-growing intracerebral gliomas, especially when anteriorly placed, is familiar to neurologists. But in such cases cerebral compression with impairment of circulation is largely local and at this stage mental deterioration is also absent.

Progressive dementia, without headache and papillœdema, may occasionally result, however, from invasion of both frontal lobes and the anterior part of the corpus callosum by an infiltrating glioma or a centrally placed meningioma, but the dissociation and its duration is again dependent upon the rate of development of the pathological process.

These examples illustrate well enough the point under discussion, but not in the same striking way as do cases of acute and chronic bilateral internal hydrocephalus in which compression of the cerebral hemisphere is general and symmetrical. When distension of the ventricles is rapid, headache is severe and associated with vomiting and weakness, and there may be loss of consciousness and convulsions. If hydrocephalus is of short duration, papillœdema is commonly absent. Acute transient attacks of this kind may occur with ball-valve tumours which block the foramina of Monro, the aqueduct of Sylvius or the fourth ventricle. When, however, ventricular blockage is very slow and progressive but variable, the process extending over a period of months or years, as in the cases which form the basis of this paper, headache, vomiting and papillœdema may be absent even at a stage when dementia or stupor, general enfeeblement and incontinence are advanced. The severity of these symptoms indicates the degree of reduction of general cerebral function from slow compression.

We are not here primarily concerned with the mechanism by which these disorders of function are produced, but the fact that great improvement may follow relief from compression by removal of its cause is in favour of the view that impairment of blood supply is the primary factor. In the causation of headache, gross variation in tension in the vessels, especially the arteries, and venous sinuses and dural septa, probably play an important part.

Lastly, I have purposely paid little attention to focal symptomatology in these two cases of third ventricle tumour, and will now mention only certain of the more important features.

In the first place, few hypothalamic symptoms were present, which is not surprising when it is remembered that the floor of the third ventricle was not directly involved by the growth in either case. Polyuria and polydipsia, adiposity or loss of weight were absent. Unfortunately, inquiry into sexual potency was omitted. In Case 1, however, transient glycosurea occurred with the first attack of unconsciousness twelve years ago, and in Case 2, excessive sweating and mild fever were present throughout the observed part of the illness. Hyperidrosis has already been described by Penfield [3] in a case of cholesteatoma of the third ventricle, as a manifestation of parasympathetic stimulation.

Abnormal drowsiness, so common with lesions in this region, was a prominent feature in both cases, Fulton and Bailey [2] believe that the neural mechanisms concerned with sleep regulation lie in the posterior part of the hypothalamus close to the midbrain. That the anterior part of the midbrain was affected in each case is shown by the pupillary abnormalities, including reflex iridoplegia. But since the lethargy appears from the first to have been associated with mental dullness it is safer to assume that it was a general rather than a focal symptom.

REFERENCES.

[1] DANDY, W. "Tumours of the Third Ventricle," Baillière, Tindal and Cox, 1933.

[2] FULTON, J. F., and BAILEY, PERCIVAL. "Tumours in the Region of the Third Ventricle," *Journ. of Nerv. and Ment. Disease*, 1929, **69**, Nos. 1, 2, 3, January, February, March.

[3] PENFIELD, W. "Diencephalic Autonomic Epilepsy," *Arch. Neur. and Psychiat.*, 1921, **22**, 358.

[4] WEISENBURG, T. H. "Tumours of the Third Ventricle," *Brain*, 1911, **33**, 236.

THE AFFERENT PATH OF THE PUPILLARY LIGHT REFLEX IN THE MONKEY.[1]

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MOST explanations of the Argyll Robertson or fixed pupil have accounted for the loss of the pupillary reactivity to light in this syndrome on the basis of a central interruption of the afferent path of the light reflex somewhere along its course to the oculomotor nucleus. A knowledge of the central course of the pathway of the light reflex has, therefore, assumed major importance for an understanding of the Argyll Robertson disorder, and in most of the publications on this subject either clinical or experimental evidence bearing on the localization of this pathway has been presented.

Extensive as this literature has been, it was not until two years ago that satisfactory evidence became available concerning that part of the arc situated within the interior of the brain. The use of a refined technique employing the Horsley-Clarke stereotaxic instrument has made it possible to fill this gap in our knowledge (Ranson and Magoun [1]), and to show that in the cat the path of the pupillary light reflex runs central from the optic tract and the superior quadrigeminal brachium to the pretectal region, or the transition area between the thalamus and superior colliculus. From the pretectal region the pathway swings ventrally around the rostral central grey matter of the aqueduct to the oculomotor nucleus, undergoing a partial decussation in the posterior commissure and another ventral to the central grey matter. It may be emphasized that the pathway was found to include the pretectal region of the brain and not the superior colliculus.

The essential rôle of the pretectal region in the innervation of the pupillary sphincter was next demonstrated in an investigation of the effect upon the light reflex of small, accurately placed lesions made with the aid of the Horsley-Clarke instrument (Magoun and Ranson [2]). In this study it was found that if the pretectal region was almost completely destroyed on both sides of the brain and the rostro-medial portion of the superior colliculus was damaged, the pupillary light reflex

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[1] Aided by a grant from the Rockefeller Foundation.

was completely and permanently abolished. Destruction of the superior colliculus alone was found to leave the light reflex intact (Magoun [3]).

The afferent path of the pupillary light reflex has thus been well established in the cat, and it seemed desirable to see if the results of these investigations could be confirmed in the primate brain. The afferent path of the light reflex, as revealed by electrical stimulation, has, therefore, been investigated in the rhesus monkey, *Macaca mulatta*, and the results obtained, which are essentially identical with those determined for the cat, form the subject of this report.

METHOD.

Stimulation of the brain-stem was performed in a series of eight monkeys, under light nembutal anæsthesia (10-16 mg. per kilo body weight), additional ether being employed during the operative preparation. One animal was a normal monkey. Each of the others had been the object of an earlier investigation of the effect of lesions in the hypothalamus or thalamus, but the presence of a pupillary reaction to light was verified in each animal before experiment, and subsequent microscopical examination of the brain demonstrated that the lesion spared the parts of the optic system concerned in every case.

In the experiments on the light reflex pathway, the skin over the top of the head was incised, 1 to 2 square inches of the vertex of the calvarium was removed, the dura was cut away, and threads were passed through the dura at the margins of the superior sagittal sinus to permit its retraction for midline stimulation. The Horsley-Clarke instrument was adjusted to the animal's head and stimulation of the brain-stem was performed. The present report is concerned exclusively with the pupillo-constrictor responses obtained, and all of these will be described with reference to the left side of the brain.

The use of the Horsley-Clarke stereotaxic instrument has been described in detail by one of us (Ranson, [4]), and the procedures involved in the present series of experiments have been almost identical with those employed in the investigation of the light reflex pathway in the cat (Ranson and Magoun, [1]). For this reason only a brief and general description of the methods need be given here. Use of the Horsley-Clarke instrument makes possible the stimulation by faradization of points within the interior of the brain, at millimetre intervals along electrode punctures, which can be subsequently identified in microscopical sections of the explored area as fine lines of hæmorrhage. By measuring from the base of these punctures, after calculating for shrinkage, the location of each point of stimulation may be determined, and a correlation made with the response obtained.

In these experiments attention was concentrated upon that portion of the brain-stem made up of the caudal portion of the thalamus, the pretectal region and the superior colliculus. The results from each of the eight animals were first worked up individually and then were plotted on a standard series of seven levels through the area explored, four of which are illustrated in fig. 1.

In stimulation of the lateral portion of the brain-stem, where the optic tract lies in relation to the geniculate bodies and pulvinar, the two electrodes, represented by the exposed tips of otherwise insulated lengths of fine nichrome wire, were separated from one another by a distance of 1 mm. along the axis of the "needle" which consisted of the two wires cemented together. The current was supplied by a single dry cell attached to a Harvard inductorium, the secondary coil of which was set sometimes at 9 cm. and sometimes at 8 cm. from the primary.

In stimulation of the more medial portion of the brain-stem (i.e. the caudal part of the thalamus, the pretectal region, and the superior colliculus from the brachium of the superior colliculus to the midline) the two electrodes were separated from one another by a distance of only 0·2 mm., and the secondary coil of the inductorium was never advanced to less than 9 cm. from the primary, and was often set at 10 cm. Such a weak faradic current, combined with the narrow separation between the electrodes, permitted the stimulation of a strictly localized area surrounding the tips of the electrodes.

RESULTS.

The pupillo-constrictor responses obtained during this series of experiments are seen (fig. 1) to fall into an orderly arrangement with reference to structures within the brain-stem, so that at least from the brachium of the superior colliculus centralward, a connected chain of responses permits the delimitation of the course taken by the light reflex fibres in their central passage to the oculomotor nuclei. It is fortunate that an abundant amount of evidence has been obtained regarding the disputed portion of the light reflex pathway from the brachium of the superior colliculus to the oculomotor nuclei, for less success has met our attempt to trace the non-controverted part of this pathway from the optic tract to the brachium of the superior colliculus.

Optic tract.—Difficulty was encountered in activating the light reflex pathway lateral to the brachium of the superior colliculus in the monkey, and even with wide-tipped electrodes and a rather strong faradic current only a small number of responses were obtained. These consisted of a slight bilateral constriction, equal in the ipsi- and contralateral pupils.

The localization of these few responses suggests that the light reflex fibres pass medially from the optic tract in the region of the lateral geniculate body (fig. 1, A) into the band of fibres which runs caudally along the lateral aspect of the medial geniculate body (fig. 1, B), and which then turns dorsally to enter the brachium of the superior colliculus (fig. 1, C and D). This small amount of evidence can do no more than suggest such a course, which, it may be noted, is comparable to that established for the cat (Ranson and Magoun [1]). No evidence has been obtained in favour of the possibility that light reflex fibres are contained in the broad tract of optic fibres which passes lateral and dorsal to the lateral geniculate body, where it joins with a prominent bundle of fibres which may represent cortical connections, from which also, no pupillo-constrictor responses have been obtained in these experiments (fig. 1, A and B).

We are unable to explain the difficulty encountered in activating the light reflex fibres in this lateral portion of the brain-stem in the monkey. It may be that the fibres take a scattered course, but even where they appear to become condensed into fairly compact strands, as on the lateral aspect of the medial geniculate body (fig. 1, B) or in the brachium of the superior colliculus (fig. 1, C and D), only slight constrictor responses have been obtained by stimulation. Stimulation of the retinal fibres in the compact optic tract peripheral to the lateral geniculate body, which was not attempted in these experiments, might be expected to yield a maximal pupillo-constriction.

Brachium of the superior colliculus.—A sufficient number of pupillo-constrictor reactions have been obtained from stimulation of the brachium of the superior colliculus in these experiments to indicate that in the monkey the afferent fibres of the pupillary light reflex reach the more medial portion of the brain-stem by way of this structure (confirming Karplus and Kreidl [5]), just as they have been demonstrated to do in the cat (Karplus and Kreidl [5]; Ranson and Magoun [1]). In the monkey, stimulation of the brachium of the superior colliculus has produced a slight bilateral constriction, equal in the ipsi- and contralateral pupils. It is perfectly clear from these experiments, however, that after reaching the brachium of the superior colliculus, the afferent light reflex fibres *do not* turn medially and caudally to enter the substance of the superior colliculus itself.

Superior colliculus.—Repeated stimulation of the superior colliculus (fig. 1, C and D) in each of the experimental animals has always failed to yield pupillo-constrictor reactions. With the more localized stimulation employed in these experiments it has been found that the pupillo-dilator responses encountered by other workers (Ferrier [6]; Karplus and Kreidl [5]) from electrical stimulation of the superior colliculus in the

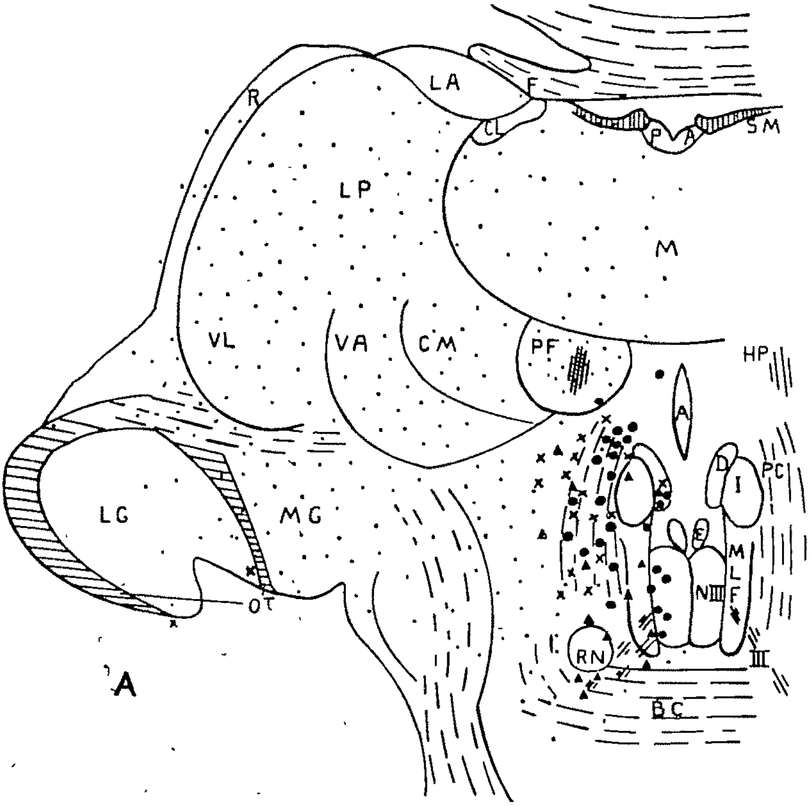
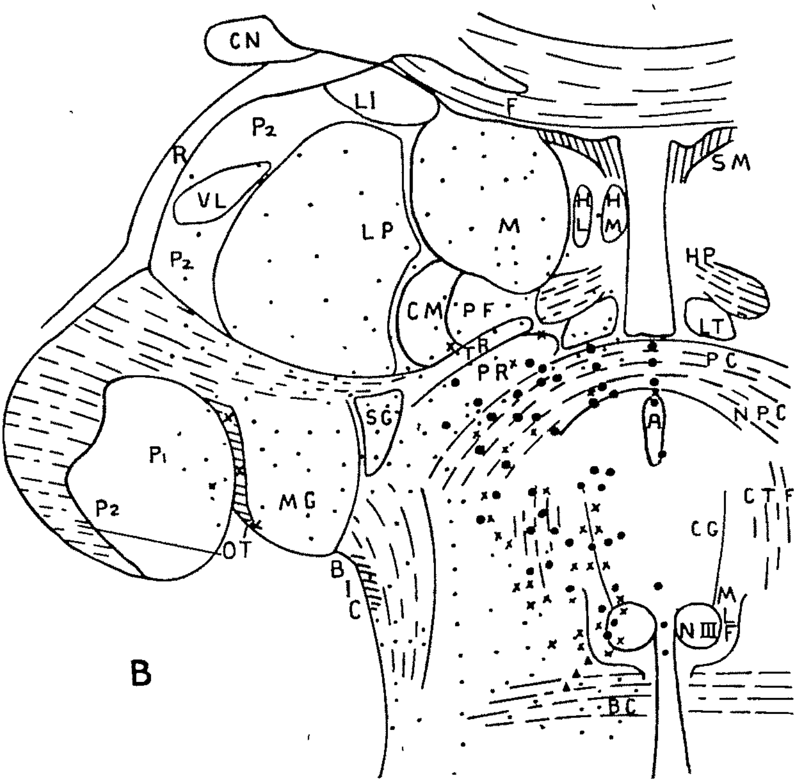


FIG. 1.—The situations of the points, stimulation of which yielded pupillo-constrictor responses in these experiments, are shown here in four levels through the left side of the brain-stem of the monkey. These levels are in the vertical plane of the Horsley-Clarke instrument, and extend serially and caudally from the caudal portion of the thalamus (A), through the pretectal region (B), to the superior colliculus (C and D). The positions in these levels of the points whose stimulation produced marked bilateral constriction are indicated by solid circles (●); the locations of points yielding slight bilateral constrictor responses

monkey, are not observed until the electrodes have been lowered through the tectum into the underlying tegmentum of the midbrain or central grey matter surrounding the aqueduct. The absence of pupillo-constrictor reactions on stimulation of the superior colliculus in the monkey is in complete agreement with the results obtained from the cat

(Ranson and Magoun [1]), and it may now be shown that in the monkey, just as in the cat, the light reflex fibres after reaching the brachium of the superior colliculus turn rostrally and medially to enter the pretectal region.

Pretectal region.—The pretectal region (figs. 1, B and 2) forms a zone of transition between the thalamus and superior colliculus, and a detailed anatomical description of its configuration in the monkey is presented elsewhere (Atlas [7]).

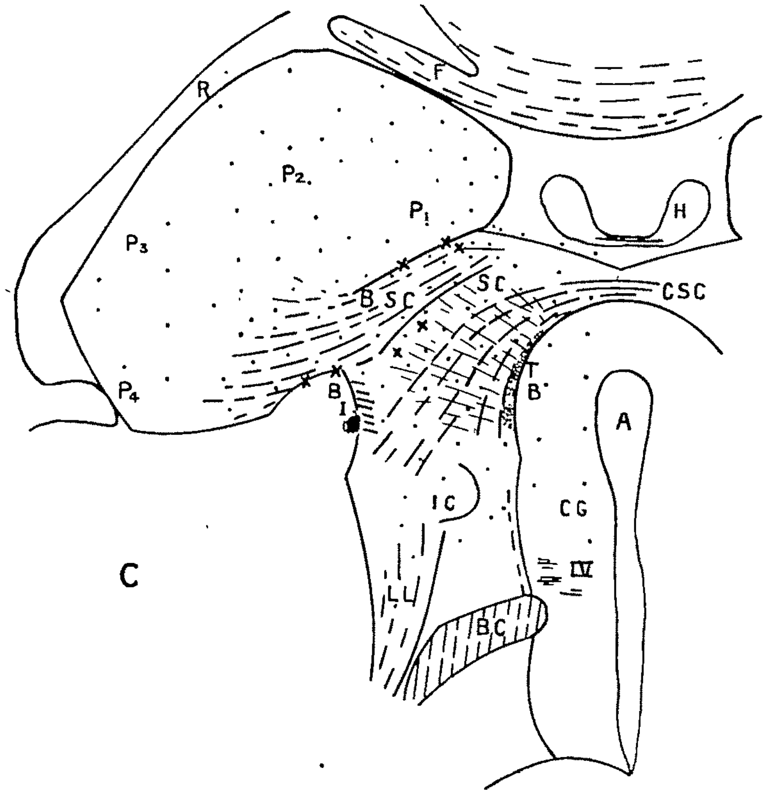


are indicated by crosses (X); and the positions of points yielding ipsilateral constrictor responses are shown by solid triangles (▲). Dots indicate the points, stimulation of which did not produce a pupillo-constrictor reaction. Level A illustrates data from 8 animals, B from 7 animals, C from 8 animals and D from 4 animals. Abbreviations for Fig. 1 are as follows:—

A, aqueduct; BC, brachium conjunctivum; BIC, brachium inferior colliculus; BSC, brachium superior colliculus; CN, caudate nucleus; CG, central grey matter; CL, nucleus centralis lateralis, CM, centre médian; CSC, commissure of superior colliculus; CTF,

In marked contrast to the inexcitability of the superior colliculus (fig. 1, C and D), stimulation of the pretectal region in the monkey (fig. 1, B), as in the cat (Ranson and Magoun [1]), has yielded a large number of pupillo-constrictor responses. These reactions in the monkey have consisted of a slight to marked bilateral constriction, equal in the ipsi- and contralateral pupils. They represent a rostro-medial continuation of the constrictor responses elicited from the brachium of the superior colliculus (fig. 1, c).

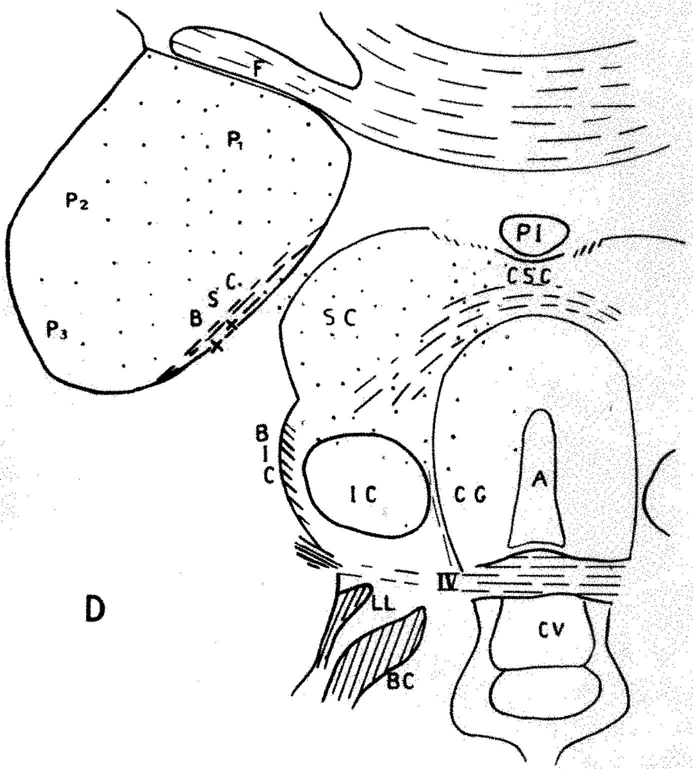
In the cat it has been shown that typical constrictor reactions are still obtainable from the pretectal region after the complete degeneration of all primary optic fibres (Hare, Magoun, and Ranson [8], and they are produced, therefore, by the activation of secondary neurones in the light reflex arc. Stated in other words, the pretectal region has been demonstrated in the cat to represent the central end-station of the



central tegmental fasciculus ; CV, cerebellar vermis ; D, nucleus of Darkschewitsch ; E, nucleus of Edinger-Westphal ; F, fornix ; H, habenula ; HL, lateral habenular nucleus ; HM, medial habenular nucleus ; HP, habenulo-peduncular tract ; I, interstitial nucleus ; IC, inferior colliculus ; LA, nucleus lateralis pars anterior ; LI, nucleus lateralis pars intermedia , LP, nucleus lateralis pars posterior ; LG, lateral geniculate body ; LL, lateral lemniscus ; LT, nucleus lentiformis thalami ; MG, medial geniculate body ; M, medial

primary optic fibres concerned in the pupillary light reflex. We see no reason to doubt the probability that this holds true also in the monkey.

The excitable area in the monkey (fig. 1, B and A) includes, in addition to the pretectal region, the posterior commissure and a broad arch around the central grey matter. This may be taken as evidence that of the fibres arising from the secondary optic neurones in the pretectal region, some cross to the opposite side of the brain in the posterior commissure, and others descend directly around the central grey matter to the oculomotor nuclei.



dorsal nucleus ; MLF, medial longitudinal fasciculus ; NPC, nucleus posterior commissure ; N III, oculomotor nucleus ; OT, optic tract ; PA, nucleus paraventricularis ; PC, posterior commissure ; PF, nucleus parafascicularis ; PI, pineal body ; PR, pretectal nucleus ; P 1, 2, 3, 4, pulvinar parts 1, 2, 3, 4 ; R, nucleus reticularis ; RN, red nucleus ; SC, superior colliculus ; SG, nucleus suprageniculatus ; SM, stria medullaris ; TB, tectobulbar fibres ; TR, nucleus of the optic tract ; VA, nucleus ventralis pars arcuata ; VL, nucleus ventralis lateralis ; III, oculomotor nerve ; IV, trochlear nerve.

Posterior commissure. — Electrical stimulation of the posterior commissure in the monkey (fig. 2) has yielded a large number of slight to marked constrictor responses, equal in the two pupils. These reactions have been obtained from fibres of the posterior commissure both in the midline (fig. 1, B), and on one side of the brain (fig. 1, B

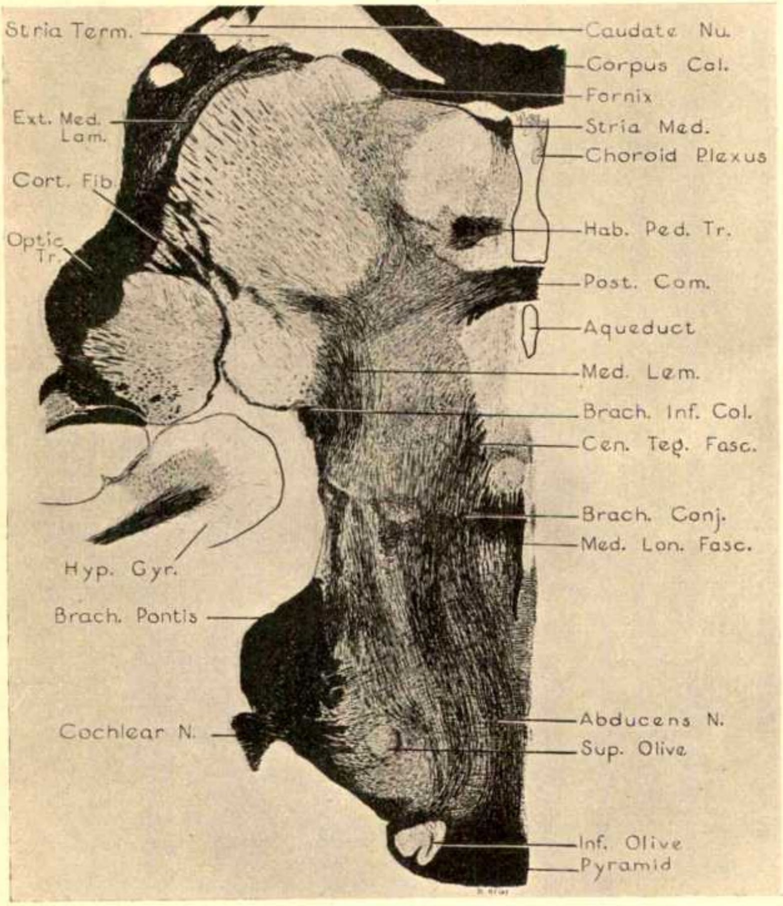


FIG. 2.—Drawing of a section stained by Weil's method through the pretectal region of the brain-stem of the monkey at the level shown in Fig. 1, B. This section is in the vertical plane of the Horsley-Clarke co-ordinates which is transverse through the thalamus, but becomes oblique through the midbrain because of the angle given to this portion of the brain stem by the cephalic flexure. The figure serves both to orient the reader and to illustrate the relationships of the myelinated fibres of the pretectal region. × 4·5. Abbreviations for Fig. 2 are as follows:—

Abducens N., abducens nerve; Brach. Inf. Col., brachium of the inferior colliculus; Brach. Conj., brachium conjunctivum; Brach. Pontis, brachium pontis; Caudate Nu., caudate nucleus; Cen. Teg. Fasc., central tegmental fasciculus; Cochlear N., cochlear nerve; Cort. Fib., cortical fibres: Corpus Cal., corpus callosum; Ext. Med. Lam., external medullary lamina; Hab. Ped. Tr., habenulo-peduncular tract; Hyp. Gyr., hippocampal gyrus: Inf. Olive, inferior olive; Med. Lem., medial lemniscus; Med. Lon. Fasc., medial longitudinal fasciculus; Optic Tr., optic tract; Post. Com., posterior commissure; Stria Med., stria medullaris; Stria Term., stria terminalis; Sup. Olive, superior olive.

and A). They unquestionably demonstrate a crossing of fibres concerned with the pupillary light reflex in the posterior commissure of the monkey, as has been previously demonstrated in the cat (Ranson and Magoun [1]).

There is no way of determining from these stimulation experiments the quantitative amount of this central decussation in the light reflex path. In the cat it has been shown to be only partial, for destruction of the posterior commissure in the midline has led to a reduction, but not to a complete abolition of the light reflex (Spiegel [9]; Magoun, Ranson and Mayer [10]; Scala and Spiegel [11]). This observation should not be applied directly to the monkey, however, for Karplus and Kreidl [5] have established the fact that the crossing of the light reflex path in the optic chiasma differs quantitatively in the cat and monkey, and the same may hold true for central decussations in this pathway.

Fibres descending around the rostral end of the central grey matter of the aqueduct.—From the pretectal region and posterior commissure of the monkey a large number of pupillo-constrictor responses may be traced ventrally around the rostral pole of the central grey matter of the aqueduct to the oculomotor nuclei (fig. 1, A and B). Some of the reactive points are situated among the descending fibres of the posterior commissure proper (fig. 1, A), while others are located in the lateral portion of the central grey matter and the adjacent fibre systems of the rostral part of the mesencephalic tegmentum (fig. 1, B.) All of the reactive points are situated rostral to the tecto-bulbar fibres (fig. 1, C). In our opinion these responses represent the activation of fibres from the pretectal region of the opposite side of the brain which have crossed in the posterior commissure, and of fibres from the pretectal region of the same side, both of which groups of fibres descend through this area to the oculomotor nuclei. Stimulation of these fibres yields a bilateral response, consisting of a slight to marked constriction, which in the larger number of cases is equal in the ipsi- and contralateral pupils, but which in some instances is greater in the pupil of the same side. In a few responses the pupil of the same side only contracted, the contralateral pupil either remaining inactive or dilating.

Ventral decussation.—The fact that bilateral pupillo-constrictor responses are obtained from stimulation of points on the lateral aspect of the central grey matter between the posterior commissure and the oculomotor nuclei (fig. 1, A and B), shows that in the monkey, as in the cat (Ranson and Magoun [1], further crossing in the light reflex pathway takes place ventral to the cerebral aqueduct. This ventral decussation could occur in the afferent path just before its synapse with the oculomotor neurones. It could also consist of inter-oculomotor connections, or of crossed efferent oculomotor fibres; or, of course, of combinations of these possibilities. The crossing would appear to be in the immediate vicinity of the oculomotor nucleus, for stimulation of points through the dorsal tegmentum up to the periphery of the oculomotor nucleus has yielded bilateral pupillo-constriction, while excitation of the root fibres of the oculomotor nerve just below the nucleus, has yielded a constriction of the ipsilateral pupil alone (fig. 1, A and B).

The impression might be gained from our first diagrammatic reconstruction of the light reflex pathway in the cat ([1], fig. 3, p. 1201), that this ventral decussation was an internuclear one, although it was stated in the accompanying text that we were unable to say whether it represented a crossing of secondary optic or of oculomotor fibres. In two subsequent publications [2, 10], this diagram has been altered to represent the ventral decussation as being made up of afferent light reflex fibres.

A comparison of the data from the monkey with those from the cat, indicates that this suggested ventral decussation is greater in the monkey than in the cat. Stimulation in the cat [12] of 141 points on one side of the central grey matter, between the posterior commissure and the oculomotor nuclei, caused constriction which was greater in the ipsilateral pupil in 88, or in about two-thirds of the responses, and in 45 of these the contralateral pupil showed no constriction whatever. In the cat constriction was equal in the two pupils in 53, or in about one-third of the reactions.

In the responses from stimulation of 118 similarly situated points in the monkey (present investigation), constriction was greater in the ipsilateral pupil in only 22, or about one-fifth of the responses, and in only 9 of these did the contralateral pupil fail to contract at all. In the reactions from the monkey, constriction was equal in the two pupils in 96, or in about four-fifths of the responses.

The results of the present investigation in the monkey do not permit the more specific localization of this presumed ventrally situated crossing of the light reflex pathway, nor do they enable us to add any information to the problem of the localization of the pupillo-constrictor component within the oculomotor nucleus itself.

DISCUSSION.

The present investigation of the path of the pupillary light reflex within the brain-stem of the monkey indicates that the light reflex fibres traverse the portion of the optic tract which runs medial to the lateral geniculate body, and passes caudally along the lateral and dorsal aspects of the medial geniculate body to reach the brachium of the superior colliculus. It is clear that after reaching the brachium of the superior colliculus the light reflex pathway does not enter the superior colliculus itself, but turns rostrally and medially into the pretectal region. From the pretectal region the pathway descends around the rostral end of the central grey matter of the aqueduct to the oculomotor nuclei. Central crossings in the path were found to occur both in the posterior commissure and ventral to the cerebral aqueduct in the immediate vicinity of the oculomotor nuclei. The course of the light reflex pathway within the brain-stem of the monkey has thus been found to be essentially identical with that previously demonstrated for the cat (Ranson and Magoun [1].

The results of our investigation of the light reflex pathway [1] have recently been vigorously criticized by Harris [13] who has suggested, on very insufficient evidence, an alternative pathway for the pupillary light reflex. In Harris' opinion the superior colliculus and tecto-bulbar fibres form the central link in the light reflex path, and this is a view which has been widely held in spite of the large amount of opposing evidence.

If the superior colliculus forms an essential part of the light reflex pathway it might be expected, first, that stimulation of the superior colliculus should cause a pupillo-constrictor response; and secondly, that destruction of the superior colliculus should abolish the light reflex. The reverse of these two considerations has been repeatedly demonstrated.

Stimulation of the dorsal surface of the superior colliculus has been found to produce a dilatation of the pupil by Knoll [14] in the rabbit; by Ferrier [6] in the rabbit, cat, jackal, dog and monkey, and by Karplus and Kreidl [5] in the cat and monkey. Our results in the cat [1] and in the monkey (see above) show that with a more localized stimulus no response from the pupil is obtained until the electrodes pass through the superior colliculus and reach the underlying central grey matter of the aqueduct or the tegmentum of the midbrain, where stimulation causes pupillo-dilatation. It is clear that stimulation of the superior colliculus does not produce a constriction of the pupil.

Furthermore, the light reflex has been found to remain intact after destruction of the superior colliculus by Knoll [14] in the rabbit, Bechterew [15] in the dog and pigeon (corpora bigemina), Gudden [16] in the rabbit, Ferrier and Turner [17] in the monkey, Levinsohn [18] in the rabbit and monkey, Bernheimer [19] in the monkey, Keller and Stewart [20] and one of us (Magoun [3]) in the cat. It is, therefore, clear that destruction of the superior colliculus leaves the light reflex intact.

Stimuli have been applied many times to the tecto-bulbar fibres in their passage through the mesencephalic tegmentum in both the cat and monkey in investigations in this laboratory, and such stimuli have never produced pupillo-constrictor responses. In this connection attention should be called to the important observation of Rasmussen [21] that in the cat efferent fibres from the superior colliculus do not terminate in the oculomotor nuclei, the tecto-fugal system being distributed chiefly to the substantia nigra, pons, the reticular formation, and to the motor nuclei of the lower portion of the medulla oblongata and the cervical segments of the spinal cord.

It is difficult to understand how, in the face of this overwhelming amount of opposing evidence, the superior colliculus and its efferent connections can still be considered the central link in the pathway for the pupillary reaction to light.

Further objection to the results of our investigation of the light reflex pathway in the cat [1] has been made by Harris [13] from the point of view of the central crossing of this path in the posterior commissure. In two experiments reported in 1904, Harris [22] observed the effect of section of the posterior commissure on the light reflex of the cat. Following operation there was a complete loss of the light reaction in his animals lasting in one case for three days. In both cases, however, the pupillary reactions returned and became, according to Harris, "quite normal."

Several factors make it difficult to estimate the value of these observations. No mention is made of the histological verification of the extent of the lesion, and without this we cannot be sure that the posterior commissure was completely divided. We have no way of knowing what a "normal" light reaction meant to Harris at the time his experiments were performed, for no measurements of the pupillary changes are given. Finally, it is impossible to learn when this return to "normal" took place, for no day-by-day records or survival times of the animals are included.

The more rigid standards employed in three recent studies of this problem have shown that while the pupillary light reflex is not abolished after complete and histologically verified destruction of the posterior commissure in the cat (Spiegel [9]; Magoun, Ranson, and Mayer [10]; Scala and Spiegel [11]), it suffers an impairment, apparent as an easily measured reduction in the amount of pupillo-constriction to a standard source of light; the five animals employed in our investigation were studied over periods of from one to four weeks after operation.

The data from stimulation experiments concur with the results obtained from these recent studies of the effects of experimental lesions in indicating that some crossing of the light reflex path takes place in the posterior commissure, for bilateral pupillo-constriction has been obtained from localized stimulation of the posterior commissure both in the cat [1, 8] and in the monkey (see above). There is no foundation for the unusual suggestion [13] that these effects are produced by a spread of current to the oculomotor nuclei over the habenulo-peduncular tract; if for no other reason, because stimulation of the habenulo-peduncular tract itself yields no response either in the cat or monkey, and effects cannot be explained as due to a spread of current to a structure which gives no response when activated directly.

It is clear, both from stimulation experiments and from critical studies of the effect of lesions in experimental animals, that some crossing of the pupillary light reflex pathway takes place in the posterior commissure. Two recent clinical studies have gone even further in ascribing a complete loss of the pupillary light reflex to destruction of the posterior commissure in man (Collier, [23]; Herrmann, [24]).

The final objection made by Harris [13] to our work [1] is related to the occurrence of a synapse in the afferent path of the light reflex. It is true that synapses were omitted in our diagrammatic reconstruction of the light reflex path (Ranson and Magoun [1], fig. 3, p. 1201), although in the description of this figure attention was called to this omission. Synapses were not shown in this diagram because at that time their location was unknown. This location has since been determined, for the first time, by stimulation of the brain-stem of the cat after the complete degeneration of all primary optic fibres, as a result of bilateral intracranial section of the optic nerves (Hare, Magoun and Ranson, [8]). The results of this investigation demonstrate that a synapse in the afferent path of the light reflex is situated in the pretectal region.

Other information pointing to the existence of this synapse, together with the importance of the central decussation in the light reflex path for an understanding of the consensual pupillary reaction, have already been considered in our review on the light reflex pathway [25]. We can find no justification for the imputation [13] that the results of our work do not account for the presence of a consensual pupillary reaction, either under normal conditions or after bitemporal hemianopsia (mid-sagittal section of the optic chiasma).

SUMMARY.

An investigation of the afferent path of the pupillary light reflex in the monkey by electrical stimulation of the interior of the brain-stem with the aid of the Horsley-Clarke instrument, indicates that the light reflex fibres traverse the portion of the optic tract which runs medial to the lateral geniculate body, and passes caudally along the lateral and dorsal aspects of the medial geniculate body, to reach the brachium of the superior colliculus. It is clear that after reaching the brachium of the superior colliculus the light reflex pathway does not enter the superior colliculus itself, but turns rostrally and medially into the pretectal region, or the transition area between thalamus and midbrain. From the pretectal region the pathway descends around the rostral end of the central grey matter of the aqueduct to the oculomotor nuclei. Central crossings in the path were found to occur both in the posterior commissure and ventral to the cerebral aqueduct in the immediate vicinity of the oculomotor nuclei.

The afferent path of the light reflex in the monkey has thus been found to be essentially identical with that recently established for the cat.

BIBLIOGRAPHY.

[1] RANSON, S. W., and MAGOUN, H. W. "The Central Path of the Pupillo-Constrictor Reflex in Response to Light," *Arch. Neurol. and Psychiat.*, 1933, **30**, 1193.

[2] MAGOUN, H. W., and RANSON, S. W. "The Central Path of the Light Reflex: A Study of the Effect of Lesions," *Arch. Ophth.*, 1935, **13**, 791.

[3] MAGOUN, H. W. "Maintenance of the Light Reflex after Destruction of the Superior Colliculus in the Cat," *Amer. Journ. Physiol.*, 1935, **111**, 91.

[4] RANSON, S. W. "On the Use of the Horsley-Clarke Stereotaxic Instrument," *Psychiat. en neurol. bl.* (Feestbund. C. U. Ariëns Kappers), 1934, **38**, 534.

[5] KARPLUS, J. P., and KREIDL, A. "Ueber die Bahn des Pupillarreflexes," *Arch. f. d. ges. Physiol.*, 1913, **149**, 115.

[6] FERRIER, D. "The Functions of the Brain," 2nd edition, London, 1886.

[7] ATLAS, D. and INGRAM, H. R. "Topography of the Pretectal Region in *Macaca mulatta*," *Journ. Comp. Neurol.* (To be published.)

[8] HARE, W. K., MAGOUN, H. W., and RANSON, S. W. "Pathways for Pupillary Constriction: Location of Synapses in the Path for the Pupillary Light Reflex and of Constrictor Fibres of Cortical Origin," *Arch. Neurol. and Psychiat.*, 1935, **34**, 1188.

[9] Spiegel, E. A. "Further Experiments on the Localization of the Argyll Robertson Phenomenon (Injuries to the Posterior Commissure)," Vol. Jubilaire en l'honneur du Professeur G. Marinesco, Bucharest, Société Roumaine de Neurologie, Psychiatrie et Endocrinologie, 1933, p. 625.

[10] Magoun, H. W., Ranson, S. W., and Mayer, L. L. "The Pupillary Light Reflex after Lesions of the Posterior Commissure in the Cat," *Amer. Journ. Ophth.*, 1935, **18**, 624.

[11] Scala, N. P., and Spiegel, E. A. "The Pupillary Reactions in Combined Lesions of the Posterior Commissure and of the Pupillo-Dilator Tracts. A Contribution to the Pathogenesis of the Argyll Robertson Pupil," *Arch. Ophth.*, 1936, **15**, 195.

[12] The data for the cat are taken from the experiments reported by Ranson and Magoun [1], and by Hare, Magoun and Ranson [8], and from unpublished observations made by Benjamin and the authors in this laboratory.

[13] Harris, W "The Fibres of the Pupillary Reflex and the Argyll Robertson Pupil," *Arch Neurol. and Psychiat.*, 1935, **34**, 1195.

[14] Knoll, P. "Beiträge zur Physiologie der Vierhügel," *Beitr. z. Anat. u. Physiol.*, 1869, **4**, 109.

[15] Bechterew, W. "Ueber den Verlauf der die Pupille verengenden Nervenfasern im Gehirn und über die Localisation eines Centrum für die Iris und Contraction der Augenmuskeln," *Arch. f. d. ges. Physiol.*, 1883, **31**, 60.

[16] von Gudden. "Demonstration der Sehfasern und Pupillarfasern des Nervus opticus," *Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol.*, 1886, **1**, 169.

[17] Ferrier, D., and Turner, W. A. "Experimental Lesions of the Corpora Quadrigemina in Monkeys," *Brain*, 1901, **24**, 27.

[18] Levinsohn, G. "Beiträge zur Physiologie des Pupillar reflexes," *Arch. f. Ophth.*, 1904, **59**, 191, and 436; "Experimentelle Untersuchungen uber die Beziehungen des vorderen Vierhugels zum Pupillarreflex," *ibid.*, 1909, **72**, 367.

[19] Bernheimer, S. "Weitere experimentelle Studien zur Kenntnis der Lage des Sphinkter- und Levatorkerns," *ibid.*, 1909, **70**, 539.

[20] Keller, A. D., and Stewart, L. "The Superior Colliculus and the Pupillary Light Reflex in the Cat," *Amer. Journ Physiol.*, 1932, **101**, 64.

[21] Rasmussen, A. T. "Tractus Tecto-spinalis in the Cat," *Journ. Compt. Neurol.*, 1936, **63**, 501,

[22] Harris, W. "Binocular and Stereoscopic Vision in Man and Other Vertebrates, with Special Reference to the Decussations of the Optic Nerves, the Ocular Movements, and the Pupil Light Reflex," *Brain*, 1904, **27**, 107.

[23] Collier, J. "Nuclear Ophthalmoplegia, with Especial Reference to Retraction of the Lids and Ptosis and to Lesions of the Posterior Commissure," *ibid.*, 1927, **50**, 488

[24] Herrmann, G. "Zur Frage der morphologischen Beziehungen des Argyll Robertson," *Allg. Zeitschr. f. Psychiat.*, 1928, **88**, 353.

[25] Magoun, H. W., and Ranson, S. W. "The Afferent Path of the Light Reflex. A Review of the Literature," *Arch. Ophth.*, 1935, **13**, 862.

CLINICAL APPLICATION OF THE CRANIO-VERTEBRAL DYNAMICS TO ENCEPHALOGRAPHY.[1]

BY THEODORE J. C. VON STORCH.

"Wherefore, in order to form a just notion of the body of man, it ought to be considered as a hydraulic machine contrived with the most exquisite art, in which there are numberless tubes properly adjusted and disposed for the conveyance of fluids of different kinds."—RICHARD MEAD, "Medical Precepts and Cautions," London, 1751.

PART I.—THEORY.

I. INTRODUCTION.—The replacement of cerebrospinal fluid by gas for diagnostic or therapeutic purposes has become an increasingly valuable neurological procedure since its introduction by Dandy [1, 2] in 1918. There are three types of subarachnoid pneumography. Myelography is the roentgenographic demonstration of the vertebral subarachnoid spaces subsequent to the replacement of cerebrospinal fluid by gas [3]. Ventriculography consists of roentgenographic demonstration of the cerebral ventricles following the direct intraventricular introduction of gas. Encephalography is the roentgenographic demonstration of the cerebral ventriculo-subarachnoid spaces following replacement of the cerebrospinal fluid by gas through cisternal or lumbar punctures.

Following the work of Bingel [4 to 9] and Wideroe [10] in 1921, lumbar encephalography has become increasingly valuable as a diagnostic and therapeutic procedure. This study is concerned solely with lumbar encephalography.

Lumbar encephalography is chiefly a diagnostic procedure, but it is occasionally used for therapeutic purposes. Its primary purpose is to make visible the intracranial ventriculo-subarachnoid spaces. Replacement of fluid by a gas is conducted through one or two needles inserted into the subarachnoid space at about the level of the fourth lumbar vertebra. Inferences may be drawn from the roentgenograms as to the condition of the brain, nerves, blood-vessels and other structures outlined by the gas. It is, therefore, of prime importance that the ventriculo-subarachnoid spaces be filled with gas in such fashion as to produce the minimum distortion of cerebral structures and at the same time a minimum reaction on the part of the patient.

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II. LITERATURE.—Any consideration of encephalography depends upon an understanding of the fundamental dynamic changes occurring in the subarachnoid space during encephalography. A review of the literature reveals only two studies on the subarachnoid dynamics of encephalography. Neither of these was based upon direct observations in man, but they were considerations of the probable sequence of events.

Castex and Ontaneda in 1932 [11 to 13] published several articles on the lumbar, cisternal and ventricular spinal fluid pressures following the replacement of cerebrospinal fluid by air. They demonstrated these changes in a glass and rubber model of the cranio-vertebral system. The apparatus used consisted of an inverted glass flask representing the cranium. A thin rubber sac representing the vertebral subarachnoid space was hung from the neck of the flask and the model was filled with water in such fashion that when erect the lumbar, cisternal and ventricular pressures accepted for man were reproduced at the proper levels. It was then demonstrated that a progressive replacement of water by equal volumes of air resulted in a decrease of the "lumbar pressure" and an increase of "cisternal and ventricular pressures" until, when the water was entirely replaced, all three pressures became the same. It was then demonstrated that if the "lumbar pressure" was maintained at its original level of 400 mm. of water[1] by replacement of the water with a larger volume of air, the other pressures gradually increased until again all three were equal, but this time at a pressure of 400 mm.

The model used was essentially that described by Propping in 1908 [14] and is too simplified to be strictly applicable to the cranio-vertebral system of man. The authors have, however, demonstrated two phenomena of cardinal importance to the practice of encephalography. The first is that during the replacement of spinal fluid by equal volumes of gas the lumbar pressure decreases, while the cisternal and ventricular pressures increase until, when completed, all become equal at a level approximating zero (atmospheric) pressure. The second is that maintenance of the original lumbar pressure during encephalography would produce a dangerously increased intracranial pressure of about 400 mm. of water in the ventricles.

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[1] Hereafter, unless otherwise indicated, pressure or force per unit area will be expressed in the normal clinical units, millimetres of water, that is that pressure which will support a column of so many millimetres of water against atmospheric pressure or 760 mm. Hg (equal to 14·6 lb per sq. in.). For example 136 mm. of water = 10 mm. of mercury = 0·19 lb. per sq. in. pressure.

Schube, in 1934 [15], published the other study dealing with the physical dynamics of encephalography. It is essentially a detailed derivation of the physical formulæ upon which is based the practice of replacing any given volume of cerebrospinal fluid by a smaller volume of gas. The formulæ are accurate, and Charles's law cannot be denied (i.e. that the pressure exerted by a given volume of gas varies directly with the temperature of the gas if the volume be kept constant). This law, however, applies to rigid containers and does not apply to pressure if the gas be allowed to change its volume. The accurate conception of the cerebrospinal fluid system is that it is not enclosed in a rigid container, but is subject to semi-rigid boundaries [16 to 26]. The author postulates that "the encephalographic procedure, therefore, consists of removing a definite volume of fluid under a relatively constant temperature and pressure *from an area with rigid boundaries* (the skull and spinal canal) and replacing it simultaneously with an equal volume of air under the same or different pressure and markedly different temperature. Hence, starting with this erroneous postulate, the author demonstrates that if room-air were made to replace an equal volume of cerebrospinal fluid, the increase in temperature would increase the pressure by 0·8 lb. per sq. in. The use of purely physical terminology has been unfortunate, as it unwittingly conceals an otherwise obvious error. This increase of 0·8 lb. per sq. in. is equal to 41·5 mm. of mercury or 564 mm. of water as expressed in clinical units. Thus an initial spinal-fluid pressure of 450 mm. of water, as measured in the sitting position at the lumbar sac, would be increased to 1,014·4 mm. of water by replacement of *any* volume of cerebrospinal fluid by an equal volume of air at room temperature. This, of course, does not occur. No such observations were made by the author during encephalography, nor have any such observations been reported in the literature. It is unfortunate that the physical arguments presented might appear to justify the old axiomatic method of replacing cerebrospinal fluid by smaller volumes of gas. One of the primary concerns of this paper is an attempt to demonstrate conclusively the error of such a procedure.

III. OBSERVATIONS.—In order to gather further evidence concerning the physiology of encephalography, experiments were conducted in connection with the encephalograms obtained in this clinic from 1932 to 1935. During this period 119 patients were investigated by the author or under his direct supervision. Each encephalogram was undertaken as a diagnostic measure, but the technique varied according to the circumstances. A preliminary report has been published [31].

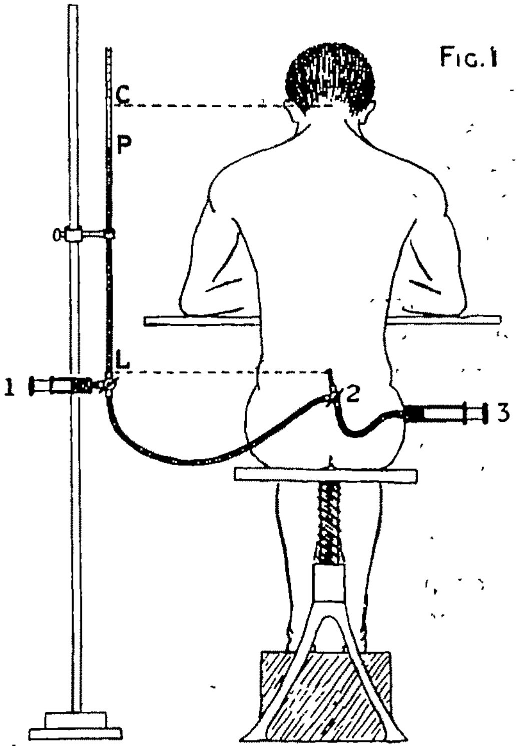

FIG. 1.—*A Method for Alternate Replacement Encephalography.* The patient sits or is supported with back anteroflexed. An Ayer-Fremont-Smith needle with attached three-way stopcock (2) is used for the lumbar puncture. Previous to measurement of pressures the 2 mm. bore open-end water manometer (C–P–L) and attached rubber tubing (L–2) is filled with sterile saline solution by the syringe (1) via the three-way stopcock at (L). With the zero level of the manometer (L) on a level with the lumbar puncture needle the meniscus in the manometer is adjusted to about level (C), and the stopcock opened to (2). Stopcock (2) is then opened to the subarachnoid space and the lumbar cerebrospinal fluid pressure is recorded. Stopcock (2) is now opened to the syringe (3) and 5 to 20 c.c. of cerebrospinal fluid allowed to flow into the syringe. Stopcock (2) is again connected with (1) and the "removal pressure" measured while the syringe (3) is disconnected and emptied into a graduate. With the syringe (3) 5 to 20 c.c. of room air is then introduced into the subarachnoid space via (2), the "replacement pressure" recorded, and the process continued until air returns into the syringe. (L) designates the lumbar, and (C) the cisternal level, while (L–P) indicates the lumbar cerebrospinal fluid pressure.

(1) *Relationship of the recumbent to the sitting cerebrospinal fluid pressure.*—In 105 cases the cerebrospinal fluid pressure was measured several days before encephalography. Lumbar puncture was performed

with the usual aseptic technique using a Fremont-Smith needle with attached three-way stopcock. Pressures were measured in millimetres of water with the Ayer-Fremont-Smith spinal fluid manometer attached directly to the needle. Throughout all the investigations the greatest care was taken to measure the pressures accurately, without loss of spinal fluid, and under standard conditions. These pressures, measured with the patient recumbent, ranged from 50 to 250 and averaged 131 mm. of water. In another series of sixty cases the lumbar cerebrospinal fluid pressure was measured immediately prior to encephalography while the patient was recumbent. The previous technique was employed except that in some cases the manometer was filled with sterile saline solution and attached to the needle by rubber tubing which was also filled with saline solution (fig. 1). These pressures ranged from 70 to 250 averaging 134 mm. of water. One hundred and six patients were then placed in the sitting position and the pressures again recorded. These latter pressures ranged from 145 to 550 averaging 371 mm. of water.

In both series it was noted that the lumbar spinal fluid pressure measured with the patient in the sitting position (371) was always greater than the pressure in the recumbent position (131). In no case was there any other relationship between the two pressures. That is, patients with low pressures when lying down might have either low or high pressures when erect, and patients with high pressures when lying down might also have either low or high pressures when sitting erect. The pressures in the sitting position appeared to bear no direct relationship to age or size of the patient. As a rule the lower pressures were found in the age group below 15, but several in this group exhibited high pressures and several low pressures were exhibited by adults.

(2) *Relation of the cisterno-lumbar distance to the lumbar cerebrospinal fluid pressure with the patient erect.*—In 100 cases the vertical distance between the lumbar puncture needle (at the fourth lumbar space) and the cisterna magna (fig. 1) was measured as well as the lumbar cerebrospinal fluid pressures of the patient when recumbent and sitting. This distance ranged from 200 to 500 and averaged 397 mm. There was a definite relation between the lumbar spinal fluid pressure in the erect position and the cisterno-lumbar distance. The difference between the two averaged only 50 mm., but ranged from minus 150 to plus 250 mm. In fifteen cases the vertical distance was less than the lumbar pressure, the difference ranging from 20 to

150 mm. and averaging 71 mm. In twenty-seven cases the distance and pressure were equal. In the majority, fifty-eight cases, the vertical distance was greater than the lumbar pressure by an average of 68 mm., the range being from 10 to 205 mm.

It should be noted that all the patients were somewhat antero-flexed so that the vertical distance measured was less than the anatomical lumbo-cisternal distance. The patients ranged in age from nine months to 64 years and there was a wide variation in length of back.

(3) *Pressure changes caused by replacement of cerebrospinal fluid by air.*—In twenty cases measurements of the lumbar cerebrospinal fluid pressure were taken after the withdrawal of each sample of cerebrospinal fluid and after the replacement of each volume of air, during the course of the entire encephalogram. The method is outlined in fig. 1. Room air was introduced slowly by syringe after withdrawal of cerebrospinal fluid. Precautions were taken at all times during the experiments to prevent leakage of air on its passage into the subarachnoid space. The apparatus was tested at frequent intervals during each encephalogram to insure that all connections were air tight. The ratio of air introduced to fluid removed (A/F) varied with each step in replacement. The total volumes replaced varied in each case, but all available cerebrospinal fluid was removed before replacement was considered complete.

In thirty-one cases of the entire series (119) an average of 13 c.c. less air was introduced (A/F less than 1); in twenty-four cases equal volumes of air replaced fluid (A/F equal to 1); and in sixty-four cases an average of 18 c.c. more air replaced fluid (A/F greater than 1) (fig. 2). The range when A/F was less than 1 was 45 c.c. to 5 c.c. less air. The range when A/F was greater than 1 was 5 c.c. to 40 c.c. more air.

In all cases the lumbar cerebrospinal fluid pressure decreased when each sample of fluid was removed and increased when air was replaced. The amplitude of these pressure changes was directly proportional to the volume of fluid removed and air replacing it at each step. In all cases, regardless of the value of A/F, the lumbar cerebrospinal fluid pressure gradually approached atmospheric pressure (fig. 2). In order to maintain a positive pressure in the lumbar subarachnoid space at completion of encephalography it was usually necessary to introduce a volume of air greater than the volume of fluid removed (A/F greater than 1). The value of A/F necessary to maintain an adequate subarachnoid pressure was an unpredictable individual variant, although it was greater than unity in the majority of cases. It was noted that when the initial spinal fluid pressure with the patient erect was low, it was necessary to increase the ratio A/F in order to maintain an adequate final subarachnoid pressure.

(4) *Effect of positional alterations on the gas-filled subarachnoid space.*—This "adequate" final lumbar subarachnoid pressure, after complete replacement of cerebrospinal fluid by air, was considered to be a pressure about equal to the previously measured lumbar cerebrospinal fluid pressure for that particular patient when recumbent. In a series of 101 cases, the lumbar subarachnoid pressures were measured with the patient sitting up after complete replacement of spinal fluid. These pressures ranged from 0 to 390, averaging 156 mm. of water. Eighty-one patients were then placed in the lateral recumbent position and the lumbar pressures measured again. The latter pressures ranged from 0 to 350, averaging 140 mm. of water. The difference between the "final sitting" and "final recumbent" pressures was calculated. It averaged 11 mm., ranging from 0 to 100 mm. of water. In no individual case was the pressure of the subject in the recumbent position after encephalography greater than the pressure in the erect position. Thus the patient sitting upright was left with a final subarachnoid pressure at the lumbar sac approximately equal to his initial pressure when lying

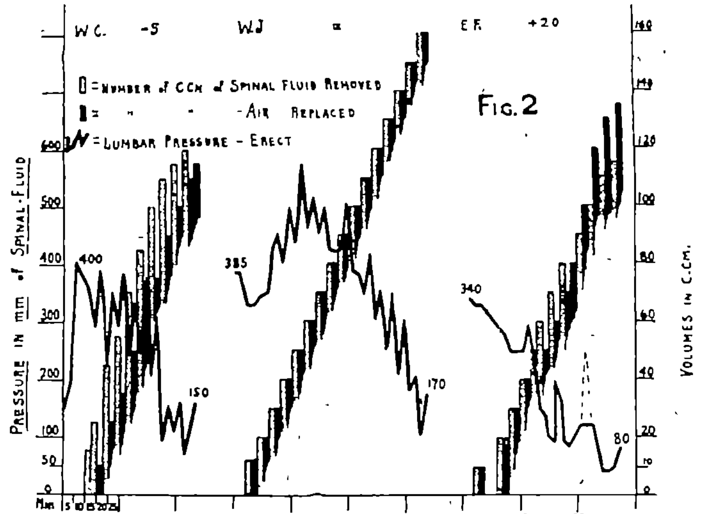

FIG. 2.—*Lumbar Cerebrospinal Fluid Pressures in Man during Lumbar Encephalography in the Sitting Position.* Three typical cases are figured showing the variations in type of curves. It will be noted that in all types the pressure irregularly but progressively decreases regardless of the relative or total volumes of fluid replaced by air.

down. This latter pressure was, therefore, present when he was returned to bed. As noted, it was necessary in the great majority of cases to introduce more air than the volume of fluid removed in order to maintain such a pressure.

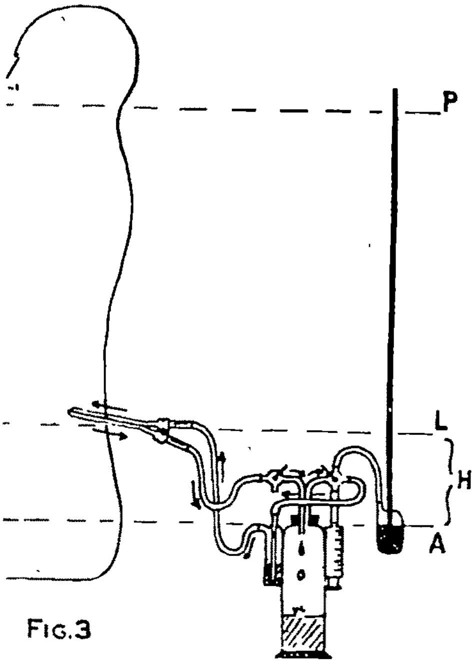

FIG.3

FIG. 3.—*An Automatic Simultaneous Replacement Apparatus for Encephalography.* Cerebrospinal fluid flows through one bore of a double needle into a closed container, displacing air from it through a sterile water bath, into the lumbar subarachnoid via the second bore of the needle. The pressure in the bottle is continuously measured by an open-end barometric type water manometer (A L P). As the bottle is placed a distance H below the lumbar needle, the pressure in the bottle A P, = L P + H. Therefore, the lumbar subarachnoid pressure L P, = A P − H when the apparatus is in equilibrium (when flow has ceased). While running the pressure A P approximates L P dependent upon the rate of flow. Thus the lumbar spinal fluid pressure may be observed at all times. By use of the syringe the volume and type of gas may be controlled as well as the pressure in the bottle or subarachnoid. After the initial adjustment replacement is automatic and alternations of pressure do not occur.

(5) *Use of an automatic simultaneous replacement method.*—As soon as the principle of replacement by pressure was conceived an apparatus[1] was devised to facilitate the technique. This apparatus is described in detail elsewhere [32]. It consists of a closed container connected with a syringe, manometer and sterile water-bath in such

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[1] Manufactured by Macalster Bicknell Company, 171, Washington Street, Cambridge, Mass.

fashion as to control the type, volume, temperature, pressure and rate of flow of the gas as well as the pressure, volume. and rate of flow of the cerebrospinal fluid (fig. 3). The apparatus was operated automatically and successfully in thirty-nine cases. When fluid was replaced in this manner the alternate decrease and increase in subarachnoid pressure was prevented (fig. 4). In the cases in which the apparatus was used

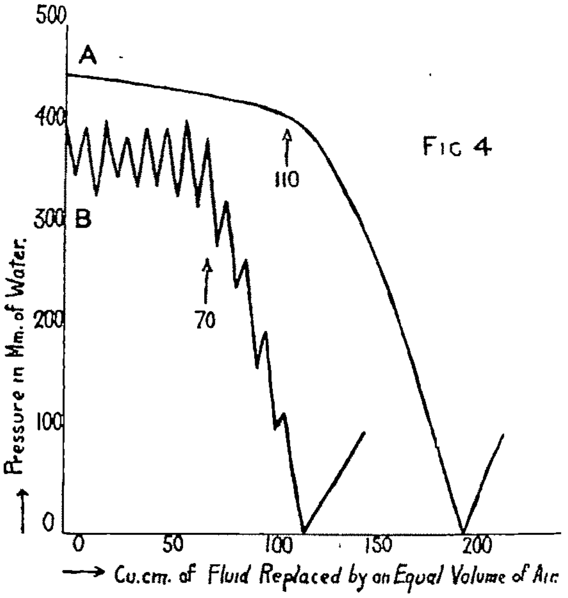

FIG. 4.—*Lumbar Cerebrospinal Fluid Pressures in Man during Lumbar Encephalography in the Sitting Position.* These curves demonstrate the marked change in *rate* of pressure decrease seen in many cases. The arrows indicate the point at which the cranium is emptied of cerebrospinal fluid. Curve A is that obtained by the simultaneous replacement method in a case with dilated ventricles and cerebral atrophy. Note the lack of pressure alternation when this method is used. Curve B is that obtained by the alternate replacement method with consequent alternation of pressures. In this case, alternations were relatively small. The intracranial volume was normal. Pressures in both cases were returned to 100 mm. by introduction of a final excess of air.

the inflammatory reaction was less marked, extravasation of blood into the fluid rarely occurred, the reaction of the patient was less severe, and the roentgenograms were more satisfactory.

(6) *Relation of the temperature of the gas to the pressure produced.*—The temperatures of all the patients at the onset of encephalography were normal (37° C.) and the room air introduced averaged 20° C. As was noted above, regardless of the value of A/F, even when an excess of air was introduced in respect to the volume of fluid removed, the lumbar arachnoid pressure decreased in all cases, approaching atmospheric

pressure regardless of the method of introduction. In no case was the increase in pressure observed, which might be expected, due to the attempt of the gas to expand as it was raised from 20 to 37° C. In a group of cases in which the simultaneous replacement method was used the air was heated by passing it through a hot water-bath before its entry into the subarachnoid. This procedure had no significant effect upon the resultant pressures.

(7) *Effect of encephalography on the composition of the cerebrospinal fluid.*—Samples of cerebrospinal fluid were taken previous to, during, and after encephalography and subjected to chemical and cytological study. In general, a lymphocytic and neutrophilic pleocytosis occurs in the cerebrospinal fluid during and subsequent to encephalography. Red blood-cells may appear occasionally due to trauma. The protein is slightly lowered and the sugar content slightly elevated. The cellular reaction was less pronounced when the simultaneous replacement method was used. All changes usually disappeared within two days.

(8) *Pressures subsequent to encephalography.*—In twenty-two cases the lumbar cerebrospinal fluid pressure was measured with the patient recumbent from one-half to forty-eight hours after encephalography (Table I). In only three of these cases was the pressure elevated above its normal value. In one of these the patient was struggling and the observations are unreliable; in another the patient developed a subarachnoid hæmorrhage several hours after encephalography. In the third case, though the pressure was elevated (190 mm. of water), the patient suffered no untoward reactions. Four other patients had a somewhat stormy course after encephalography, but their pressures were rather lower than increased (150, 70, 30 and 30 mm. of water).

(9) *Reaction of the patient to encephalography.*—In eighty-two cases a general anæsthetic was used during encephalography. The anæsthetics used were avertin, 100 mgm. per kilo body weight per rectum, or nembutal, 3 to 10 gr. intravenously. In these patients, especially those anæsthetized with nembutal, the subsequent reactions were somewhat less severe than in the unanæsthetized patients. These anæsthetics have little or no effect on patients accustomed to the use of barbiturates. Therefore, in twenty-two cases light morphine and scopolamine narcosis was employed, and in fifteen cases no narcosis was used. These patients complained of headache during the introduction of the first 10 c.c. of air. Withdrawal of fluid occasioned no complaint.

The reactions encountered during the replacement of fluid were: Low pulse pressure, tachycardia, cyanosis, hypernœa, hyperhydrosis, nausea and vomiting, and rarely a fall in blood-pressure. In cases in which the anæsthetic had occasioned a fall in blood-pressure, the introduction of the first few cubic centimetres of air caused it to return to normal. Subsequent to encephalography the same chain of phenomena were seen in lesser degree, added to which were headache, stiff neck, hyperpyrexia (102° to 104° F.) and low skin temperature. The signs and symptoms were much less apparent when the simultaneous replacement method was used. Low blood and pulse pressures, vomiting and chills were rare. The hyperpyrexia was diminished and shortened, and the headache was much less severe.

Shock occurred in eight cases during encephalography. All of these were subjected to the syringe method of alternate replacement; six patients exhibited high lumbar cerebrospinal fluid pressures, and four were "brain tumour suspects." Shock occurred after encephalography in four cases, three of whom were "brain tumour suspects," two exhibited high spinal-fluid pressures, and two were over 50 years of age. One of these cases was a 52-year-old "brain tumour suspect" who developed a subarachnoid hæmorrhage several hours after encephalography. The simultaneous replacement method was used in two of the brain tumour suspects; in these shock occurred. There has been no fatality in this clinic to date.

The temperature and the relative or total volumes of gas used had no bearing upon the patient's reactions during or subsequent to encephalography. Room air was used in all cases. Those cases that presented a severe reaction to the procedure were analysed carefully. In one case, the spinal fluid pressure was increased after encephalograpy. The clinical appearance of the cases resembled the combined picture of surgical shock with superimposed meningeal irritation. The cerebrospinal fluid cell counts were often high in such patients for more than forty-eight hours after encephalography. Cases with dilated ventricles tended to recover more slowly than those with normal-sized ventricles and with less comfort than "normals."

(10) *Roentgenographic results.*—The roentgenographic results were analysed in all the cases with especial reference to the degree of replacement of intracranial cerebrospinal fluid and the distribution of the air. It was found that the ventricular outlines as well as the cisternal and convolutional markings were demonstrated more completely and clearly in those cases in which the ratio A/F was definitely greater than unity. That is, the reliability of the roentgenograms varied directly with the relative volume of air introduced. Manipulation of the head was, of

course, an important factor in producing adequate replacement. In twenty cases, the air demonstrated incompletely the cerebral structures. None of these cases was done by the simultaneous method: in twelve the ratio A/F was less than 1; in four it was equal to 1, and in only three was it greater than 1. In four cases no air at all could be demonstrated in the head. In one of these the apparatus leaked, and in two air was demonstrated in the neck up to the cisterna magna, but no block could be demonstrated.

IV. DISCUSSION.—Loman, Myerson and Goldman [16 to 19] have made an extensive study of the lumbar and cisternal cerebrospinal fluid pressures of man in the recumbent, erect and sitting positions as well as measurements of the internal jugular pressures. They feel that the lumbar cerebrospinal fluid pressure is a direct reflection of the venous pressure at that point. Their work is very suggestive but not conclusive.

Weed and his co-workers [20 to 29] have investigated the relationship of postural change to cerebrospinal fluid and venous pressure in animals. They have concluded that there are two factors determining the pressures. One is the meningeal element determined by dural elasticity, which is active in the vertebral canal but negligible in the cranium. The other is the vascular element which is modified by autonomic tone and elasticity of the vessel walls. Both of these factors act synchronously, but only the predominant factor is responsible for the measurable cerebrospinal fluid pressure according to the type and position of the preparation. They conclude that the vascular factor, which is a reflection of the intradural venous pressure, is responsible for the intracranial pressure in the head-down vertical position but that the meningeal factor, allowing dislocation of cerebrospinal fluid, is predominant in the normal head-up position. The use of occipital and sagittal punctures, and of quadripeds in their crucial experiments, detracts from the value of their observations in interpretation of the lumbar pressures in man.

The present observations have shown that although the lumbar cerebrospinal fluid pressure in the sitting position is always greater than in the recumbent position it bears no direct relationship to the latter. This suggests that the pressure in the erect position is not composed of the recumbent pressure plus some factor x, but is entirely due to changes subsequent to postural alteration. Because of the wide variability of the relationship of the two pressures it is unlikely that the lumbar cerebrospinal fluid pressure in the erect position is largely determined by dural elasticity. Clinical observation of the patients during encephalography suggested a wide range in venous pressures during the procedure. It was also observed that although in the majority of cases the vertical lumbar-cisternal distance was greater than the lumbar cerebrospinal fluid pressure, in some they were equal and in others the lumbar cerebrospinal fluid pressure was greater than this distance. This suggests that the column of cerebrospinal fluid from the needle to the cistern is not the determining factor. Here again the wide range suggests some facile factor. It is suggested, therefore, that the lumbar cerebrospinal fluid pressure of man in the erect position may be determined by the lumbar intradural venous pressure in the smaller veins and venules at that level.

Removal of cerebrospinal fluid will produce a progressive venous dilatation until restrained by the elasticity of the vessel walls. At this point the system becomes rigid toward sub-atmospheric pressures and cerebrospinal fluid will not run freely from the lumbar subarachnoid. The system is, therefore, not completely elastic. By introduction of air at this point, or by alternate replacement, the system may be emptied of cerebrospinal fluid. As air is replaced at atmospheric pressure the lumbar cerebrospinal fluid pressure must, therefore, progressively decrease until, at complete replacement, the pressure is atmospheric at the lumbar sac. This was observed to be true. At this point all veins in the system in which the pressure is above atmospheric, must be dilated. A certain proportion of the intracranial veins may not dilate, however, as their pressure is lower.

It was observed that alternate removal of cerebrospinal fluid and replacement with air, produced alternating decreases and increases in the lumbar cerebrospinal fluid pressure proportionate to the volumes replacing each other (fig. 2). Such pressure changes are transmitted in the cerebrospinal fluid system to the intracranial cavity. Thus each decrease would produce venule dilatation and cyanosis and possibly arteriolar constriction as has been demonstrated in cats by Forbes [30]. Increase in pressure reverses the procedure and hence a cerebral "massage" occurs during replacement. This is conducive to hyperæmia, œdema and hæmorrhage.

It was deemed advisable to produce a standard intracranial pressure during roentgenography in order that comparative observations may be made in various individuals from time to time. Without such a standard, encephalograms are not comparable even in the same individual. This standard was determined as the intracranial pressure normal for that individual at the time of encephalography when measured in the *recumbent* position.

When the cerebrospinal fluid has been "completely" replaced by air, the ventriculo-subarachnoid system is no longer a hydrodynamic but an aerodynamic or gas system in which pressures at all points are equal. Hence, the lumbar subarachnoid pressure is equal to the intracranial pressure. As the gravitational effect on such a system is infinitesimal the pressures remain the same regardless of the angle of the system with the horizontal. It will be seen, therefore, that if the final lumbar subarachnoid pressure, measured with the patient erect, be made equal to the lumbar cerebrospinal fluid pressure measured in the recumbent position previous to encephalography, the "normal recumbent" intracranial pressure will be produced with the patient erect.

In maintaining such a pressure, the ratio of air replaced to fluid removed (A/F) was quite variable, but in the great majority of cases A/F was greater than unity. It was observed that not only was there no increased intracranial pressure following replacement of equal volumes, but also there was no increased intracranial pressure when the replacing air exceeded the fluid removed (A/F greater than unity).

The replacement of any given volume of fluid from a rigid container at 37° C. with an equal volume of gas at 20° C. (room temperature) would produce an increased pressure. It has been apparent to all observers that the cranio-vertebral container of the cerebrospinal fluid system is semi-rigid in character. It was observed that assumption of the sitting posture by man results in an expression of an additional volume of cerebrospinal fluid into a lumbar manometer. Consequently, the measurable increase in lumbar spinal fluid pressure is merely confirmatory evidence of the non-rigid character of the container. A rigid container less than 32 ft. in length filled with fluid approximating the specific gravity of water (1·007) would not allow the fluid to run from it when changed from the horizontal to the vertical position. The observation that free flow of fluid from the subarachnoid ceases when atmospheric pressure is reached and *before* the subarachnoid is emptied confirms the views that the container is not completely elastic (open to atmosphere). A completely elastic container could not support such sub-atmospheric pressures as must exist at levels above the lumbar needle after flow has ceased. Therefore, being neither rigid nor elastic the system must be semi-rigid. The elasticity of such a system depends either upon the meningeal or vascular element [20 to 29]. Such elasticity is an individual variant.

Measurements of the cerebrospinal fluid pressure during and after encephalography have conclusively demonstrated that it is *not* necessary to withdraw more fluid than the volume introduced in order to prevent an increased intracranial pressure. It was observed that the lumbar cerebrospinal fluid pressure decreased during encephalography regardless of the amount of gas introduced relative to the volume of fluid removed. There are two factors responsible for the prevention of increased intracranial pressure. The oxygen component (20 per cent.) of the air introduced is absorbed rapidly, thus reducing intracranial volume and pressure. Even if absorbed instantly this 20 per cent. decrease in volume would only neutralize the effect of the excess air introduced, as the volume of air introduced was often 20 per cent. greater than the volume of fluid removed. The second factor is that expansion of the gas, as it is raised to body temperature, is possible in the semi-rigid cranio-vertebral container of man. Expansion occurs by means of a diminution in intravascular volume within the system. Only 5 c.c. of blood need be expressed from the entire cranio-vertebral vascular system to allow for the replacement of equal volumes when introduced at atmospheric pressure and room temperature. Such a loss of blood volume does not appear to be hazardous. Both expansion and absorption are at work; which factor predominates is only of academic interest. The fact remains that throughout this series the volume of air introduced was often greater than the volume of fluid it replaced without the production of increased spinal fluid pressures or undue signs and symptoms.

As the elasticity of the cranio-vertebral container is an individual variant, volumetric changes cannot be used as indices of the pressures produced thereby. The cerebrospinal fluid pressures must be directly observed. We may therefore cease to pay much attention to the *volume* of air introduced in encephalography, focusing attention on the pressures themselves.

It must not be inferred that the production of a final lumbar subarachnoid pressure in the sitting position, which is equal to the normal pressure lying down, does not increase the usual intracranial pressure of the patient while sitting up. All pressures are equal in the gas-filled system and hence during roentgenography the intracranial pressure is at the normal level for recumbency (about 130 mm. of water) instead of at its normal of about minus 100 mm. of water. Thus, roentgenograms are made of the ventriculo-subarachnoid system under the pressure and volume relationships which exist normally in the recumbent position. A much more accurate picture is thus produced, as vascular engorgement of the subarachnoid space is prevented. The roentgenograms are much better than by the older procedure and "incomplete filling" is a rarity.

At the conclusion of encephalography, when all the fluid has been replaced, the ventricular, cisternal and lumbar pressures are identical whether the patient be sitting or recumbent. Therefore, if a normal lumbar subarachnoid pressure be produced in such a system while the patient is sitting up, the pressure will remain the same when the patient is returned to bed. Consequently, the ventricular pressure will remain the same and the patient will be returned to bed with the same intracranial pressure which existed before encephalography. The measurements of the final lumbar pressures with the patient erect (156 mm.) and the final lumbar pressures with the patient lying down (140 mm.) show this to be true. When any difference occurred, the lumbar pressures in the recumbent position were slightly less (11 mm.) than the final pressures when sitting up. This is due either to incomplete drainage, in which case the small amount of fluid exerted a pressure in the sitting position, or to the fact that the venous pressure decreased in the recumbent position.

The results of studies on the cytology and chemistry of the cerebrospinal fluid during and subsequent to encephalography present additional evidence that simultaneous replacement produces less physiological disturbance than alternate replacement. When the alternation of pressures is removed by use of this method, red blood cells are rarely found in the spinal fluid, while leucocytes average 15 to 20 per c.c. rather than 200 to 400 by the former method. It would thus appear that much less meningeal irritation results from the simultaneous replacement method.

After encephalography has been completed, two series of reactions are set up which determine the subsequent intracranial pressure. The presence of the air with its consequent meningeal irritation very likely produces an increased rate of production of the cerebrospinal fluid. The removal of fluid also increases its rate of production. These factors are conducive to an increased intracranial pressure. On the other hand, the absorption of the air tends to reduce the pressure. Its oxygen content (20 per cent.) is absorbed rapidly, the inert gases more slowly. In addition, if the patient is in a state of shock (which is unusual) the venous pressure is low, thus increasing absorption. These factors tend to decrease the intracranial pressure. The pressure subsequent to encephalography is determined by the relative value of these forces. The observations presented in this investigation demonstrate that the forces tending to decrease the subsequent cerebrospinal fluid pressures are predominant.

Even in the patients who presented a severe reaction subsequent to encephalography, measurement of the cerebrospinal fluid pressure demonstrated that the pressure usually was decreased rather than increased.

Analysis of the clinical features of the patients' reactions to encephalography show them to fit much better into the picture of surgical shock combined with a meningeal reaction. The low blood and pulse pressure, tachycardia and cold sweat suggest shock, while the hyperpyrexia, stiff neck, headache and vomiting are indicative of meningeal irritation. The cerebrospinal fluid pressures were not increased.

During the measurements of the lumbar cerebrospinal fluid pressure while the cerebrospinal fluid was being replaced volume for volume by syringe it was noted that the pressure decreased slowly at first and then suddenly began a rapid descent. This would be expected if the height of the column of fluid were a factor in producing the pressures. For every volume of fluid replaced from the relatively greater intracranial fluid spaces, the decrease in the height of the column would be less than when an equal volume of fluid was being replaced from the slender vertebral tube. It may be inferred that the change in rate of decrease of pressure occurs when the intracranial cerebrospinal fluid spaces have been emptied. It is theoretically possible, therefore, to accurately estimate the volume of intracranial cerebrospinal fluid in man. The procedure is as follows :—

Perform a lumbar puncture with the patient sitting erect and replace the cerebrospinal fluid by air, volume for volume, measuring the lumbar cerebrospinal fluid pressure after the introduction of each volume of air. Note the point where the pressure begins to decrease rapidly and continue replacement to confirm this observation. The volume of cerebrospinal fluid removed at this point should then equal the intracranial cerebrospinal fluid volume. The head should be manipulated during replacement to assist in complete evacuation of the ventricles.

During encephalography it should, therefore, be possible to obtain complete replacement of intracranial cerebrospinal fluid without continuing the replacement of intravertebral fluid. In a number of cases, this procedure was followed by excellent roentgenographic results.

Replacement was stopped when the pressure began to decrease rapidly and consistently. Either syringe or simultaneous methods are applicable. Several unsuspected cases of ventricular dilatation and cerebral atrophy were thus diagnosed previous to roentgenography by observing the volume of intracranial fluid. These suspicions were confirmed by roentgenography.

V. APPLICATION.—Many of these principles have been applied to the practice of encephalography with excellent results. These have been discussed in a separate investigation [32] and are briefly outlined herein that their relation to the dynamics may be more apparent.

(1) A complete lumbar puncture study should be performed previous to encephalography and the lumbar cerebrospinal fluid pressure in the recumbent position recorded for use during encephalography. The studies of the dynamics, cytology, chemistry and serology of the cerebrospinal fluid obtained from this puncture may contra-indicate or render unnecessary the subsequent encephalography.

(2) Encephalography is contra-indicated in the presence of a lumbar cerebrospinal fluid pressure in the recumbent position greater than 200 mm. of water or when signs of increased intracranial pressure are apparent. It is dangerous when weak-walled anomalies of the cerebral vascular bed are present.

(3) Anæsthesia or deep narcosis is an aid to patient and operator. Ether, ethyl chloride, nitrous oxide and other inhalant anæsthetics produce a dilatation of cerebral vessels increasing the pressure and preventing adequate filling, and are, therefore, contra-indicated.

(4) The best approach to the subarachnoid space is by lumbar puncture. The single puncture method is recommended only in the case of infants or when a double puncture needle[1] is not available. The use of such a double needle or of two lumbar punctures is recommended as simultaneous replacement may be carried out only through two aperatures.

(5) Some form of simultaneous replacement is recommended. The automatic apparatus is easiest to use and controls all the necessary factors. Only by simultaneous replacement may the alternations of intracranial pressure be prevented and with them the untoward reaction of the patient.

(6) Ordinary air at room temperature is recommended as the gas of

[1] Manufactured by Randall-Faichney, Inc., 128, Heath Street, Boston, Mass.

choice. It may be filtered through hot or cold sterile water, if desired. The amount of gas used is a variable, depending entirely upon the pressures produced during replacement. It is, therefore, unnecessary for practical purposes to record the volume of air introduced.

(7) All obtainable cerebrospinal fluid should be replaced by a volume of gas which produces a lumbar subarachnoid pressure in the *sitting* position approximating to the previously recorded lumbar pressure for that patient in the *recumbent* position. In order to do so it is usually necessary to introduce a volume of air greater than the volume of fluid it replaces. By such means the encephalograms for any series of cases are given a common basis and are hence subject to comparative studies, a condition which does not now exist.

(8) During replacement the patient's head should be slowly and continuously antero- and postero-flexed in order to evacuate the ventricles. Lateral flexion is contra-indicated as it predisposes to unequal distribution of the supra-cortical air.

(9) Some supportive apparatus is of great value in managing the anæsthetized patient [33].

(10) The entire procedure from puncture to picture should be performed with the patient sitting erect. In cases of suspected temporal or occipital lobe tumours, the appropriate roentgen exposures may be made in the recumbent position after the exposures have been made while the patient is sitting up.

CONCLUSIONS.—A. It has been demonstrated that:—

(1) The cranio-vertebral container of the cerebrospinal fluid system of man is semi-rigid.

(2) The cerebrospinal fluid system is subject to pressure alterations dependent upon its angle from the horizontal and upon pressure changes in its vascular components.

(3) The lumbar cerebrospinal fluid pressure measured with the patient sitting up closely approximates the vertical cisterno-lumbar distance for that patient, and bears no relation to the pressure measured in the recumbent position.

(4) Since the elasticity of the cranio-vertebral system is an individual variant, volumetric computations cannot be used as indices of expected pressure changes occurring in the ventriculo-subarachnoid spaces. Observations of such pressures must be made directly.

(5) Replacement of cerebrospinal fluid (by syringe) through a

single lumbar puncture produces alternate elevation and depression of the cerebrospinal fluid pressure. Simultaneous replacement of cerebrospinal fluid prevents these alternations and minimizes the patient's unfavourable reactions.

(6) When the cerebrospinal fluid has been completely replaced by gas, the ventriculo-subarachnoid space is a gas-filled system in which pressures at all points are equal irrespective of position. Therefore, the lumbar subarachnoid pressure in such a system remains the same whether the patient be sitting or recumbent, and consequently the intracranial pressures are unchanged.

(7) The production of a final lumbar subarachnoid pressure, after complete replacement of the cerebrospinal fluid by a gas, which approximates the normal lumbar cerebrospinal fluid pressure for that patient when recumbent is not dangerous. It results in excellent roentgenograms under normal pressure-volume relationships and does not increase the patient's reaction.

(8) It is possible to introduce a volume of air at room temperature (20° C.) greater than the volume of cerebrospinal fluid removed (at 37° C.) without significantly increasing the intracranial pressure.

(9) The introduction of a volume of air greater than the volume of fluid it replaces increases the reliability of the roentgenograms.

(10) Subsequent to encephalography, after the manner outlined, the cerebrospinal fluid pressure is not increased above its normal value. The untoward reactions occasionally occurring are not due to increased intracranial pressure.

B. It is highly probable but as yet unproven that :—

(1) Alternate replacement of cerebrospinal fluid by a gas through a single aperture produces alternate vasoconstriction and vasodilatation of the cerebral vascular bed with hyperæmia, œdema, hæmorrhage and severe reactions on the part of the patient.

(2) The reactions of the patient subsequent to encephalography are not due to increased intracranial pressure, but to shock and meningeal irritation.

(3) When the cerebrospinal fluid begins to decrease rapidly during replacement of the fluid by an equal volume of gas, the volume of fluid removed is then equal to the volume of intracranial cerebrospinal fluid.

The proper performance of encephalography depends not so much on the technique or apparatus as upon a thorough understanding of the underlying dynamic principles and their physiological results.

TABLE I.

LUMBAR CEREBROSPINAL FLUID PRESSURES DURING AND AFTER ENCEPHALOGRAPHY.

LUMBAR CEREBROSPINAL FLUID PRESSURES :

No of c.cm.		Csf. minus Air	Initial		Final		After Encephalography							Reaction of Patient
Csf.	Air		Rec.	Sit.	Sit.	Rec.	½ hr.	1 hr.	4 hrs	6 hrs	12 hrs	24 hrs.	48 hrs.	
130	105	— 25	110	450	150	150		30						Poor.
120	100	— 20	110	350	100							30		,,
120	100	— 20	130	400							70			,,
115	95	— 20	130	420	250	200				80				Good.
135	120	— 15	170	140								80		,,
110	95	— 15	200	400	200	200					140			,,
87	75	— 12	100	375	110	100	30	20						,,
30	20	— 10	110	300	120	110				110			50	,,
110	100	— 10	150	475						0				,,
120	115	— 5	150	400	150	140				90				,,
70	65	— 5	85	400	100	90					190			,, [1]
100	125	— 5	110	400	130	130			110					,,
100	100	0	90	375	200	180							120	,,
50	50	0	150	400	150	150				150			50	Poor.
70	75	+ 5	100	500	200	150				110		50		Good.
100	110	+ 10	110	450	150	140	20							,,
107	117	+ 10	190	420	200	190						190		,,
90	100	+ 10	175	450	200	175			175	190		210		Poor.[2]
100	120	+ 20	130	550	130	120					310	400		Shock.[3]
95	115	+ 20	150	350	250	200		150		200		85		Good.
120	145	+ 25	130	440	150	150			30					,,
130	160	+ 30	150	400	150				70					,,

Csf.—Number of c.cm. of Cerebrospinal Fluid removed.
Air.—Number of c cm. of Air replacing Fluid.
Rec.—Pressure with Patient Recumbent.
Sit.—Pressure with Patient Sitting.
Initial.—Pressure measured immediately previous to Encephalography.
Final.—Pressure measured immediately after Encephalography.

All other pressures were measured from ½ to 48 hours after encephalography and all were measured with the patient recumbent.

[1] Increased pressure but good recovery.
[2] Patient struggling during Pressure Measurement.
[3] Subarachnoid Hæmorrhage after Encephalogram.

BIBLIOGRAPHY.

[1] DANDY, W. E. *Ann. Surg.*, 1918, **68**, 5.
[2] *Idem. Ibid.*, 1919, **70**, 397.
[3] COGGESHALL, H. C., and VON STORCH, T. J. C. *Arch. Neurol. and Psychiat.*, 1934, **31**, 611.
[4] BINGEL, A. *Deutsch. Zeitschr. f. Nervenheilk*, 1921, **72**, 359.
[5] *Idem. Deutsch. med. Wchnschr.*, 1921, **47**, 1492.
[6] *Idem. Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1921, **28**, 205.
[7] *Idem. Deutsch. Zeitschr. f. Nervenheilk.*, 1922, **74**, 121.
[8] *Idem. Klin. Wchnschr.*, 1922, **1**, 2191.
[9] *Idem. Med. Klin.*, 1923, **19**, 637.

[10] Wideroe, S. *Zentralbl. f. Chir.*, 1921, **48**, 394.
[11] Castex, M. R., and Ontaneda, L. E. *Rev. Asoc. Med. Argent.*, 1932, **46**, 342.
[12] *Idem.* *La Prensa Med. Arg.*, 1932, No. 30, **18**, 1427.
[13] *Idem.* *Ibid.*, 1932, No. 31, **18**, 1473.
[14] Propping. *Mitteilungen aus d. Grenzgeb.*, 1908, **19**. Quoted by Pappenheim, M., "Lumbar Puncture," New York, Wm. Wood & Co., 1925.
[15] Schube, P. G. *Journ. Nerv. and Ment. Dis.*, 1934, **80**, 291.
[16] Loman, J., and Myerson, A. *Arch. Neurol. and Psychiat.*, 1932, **27**, 1226.
[17] Myerson and Loman. *Ibid.*, 1932, **27**, 836.
[18] Loman, J. *Ibid.*, 1934, **31**, 679.
[19] Loman, J., Myerson, A., and Goldman, O. *Ibid.*, 1935, **33**, 1279.
[20] Weed, L. H. *Amer. Journ. Anat.*, 1923, **31**, 191.
[21] *Idem.* *Arch. Surg.*, 1929, **18**, 1049.
[22] Weed, L. H., and Flexner, L. B. *Johns Hopkins Hosp. Bull.*, 1932, **50**, 196.
[23] Weed, L. H., Flexner, L. B., and Clark, J. H. *Amer. Journ. Physiol.*, 1932, **100**, 246.
[24] Weed, L. H., and Flexner, L. B. *Amer. Journ. Physiol.*, 1932, **101**, 668.
[25] Flexner, L. B., Clark, J. H., and Weed, L. H. *Ibid.*, 1932, **101**, 292.
[26] Weed, L. H. *Physiol. Rev.*, 1933, **13**, 80.
[27] Weed, L. H., and Flexner, L. B. *Amer. Journ. Physiol.*, 1933, **105**, 266.
[28] Flexner and Weed. *Ibid.*, 1933, **104**, 681.
[29] *Idem.* *Ibid.*, 1933, **105**, 571.
[30] Forbes, H. S., and Nason, G. I. *Arch. Neurol. and Psychiat.*, 1935, **34**, 533.
[31] von Storch, T. J. C. *New England Journ. Med.*, 1934, **211**, 773.
[32] *Idem.* *Amer. Journ. Roentgenol. and Radium Therapy*, 1936, **35**, 78.
[33] Epstein, S. H., and von Storch, T. J. C. *Amer. Journ. Roentgenol. and Radium Therapy*, 1935, **34**, 451.

NOTICES OF RECENT PUBLICATIONS.

Indications Opératoires D'urgence dans les Lésions Traumatiques Fermées Récentes du crane et de L'encéphale. Par A. JENTZER. Paris : Masson et Cie. 1935. Pp. 105. Price 25 francs.

In this monograph, Jentzer has analysed all the cases of head injury which have entered the surgical clinic of the University of Geneva between the years 1914 and 1934. The bulk of the monograph is occupied by the brief descriptions and statistical analyses of these cases, which numbered 837.

The author summarizes his experience. More than 50 per cent. of the cases, many of them grave, recovered without surgical intervention. He regards this as a triumph for the conservative method.

He also sets out the indications for surgical intervention. These are the appearance of the following signs after a "free interval" of varying duration during which simple coma without localizing signs has been present: *Unilateral mydriasis.* This is invariably associated with a homolateral hæmatoma or gross cerebral lesion. *Localizing signs*, such as cranial nerve palsies, hemiplegia, monoplegia, Jacksonian fits, and a unilateral Babinski response. *Unilateral exophthalmos.* The progressive development of areflexia, slow pulse, loss of pupillary light reaction, fever, intracranial hypertension, persisting coma and stertorous breathing.

This careful record of the extensive practice of a single clinic by one observer lends the monograph a value and importance which must commend it to the neurosurgeon.

Les Syndromes Neuro-hématiques. Par H. ROGER et J. OLMER. Paris : Masson et Cie. 1936. Pp. 225. Price 32 francs.

Professor Roger and his collaborator have in this monograph given a concise summary, clinical and pathological, of the various affections of the nervous system that are found in association with altered blood states.

Appropriately, the largest section is devoted to subacute combined degeneration of the cord, its ætiology, symptomatology, course, morbid anatomy and treatment.

Other sections deal with polycythæmia, the leukæmias, lymphadenoma, and the effects upon nervous function of severe hæmorrhage.

The reader will find the monograph comprehensive and embodying the most recent advances in knowledge.

Les Encéphalites Aiguës Post-Infectieuses de L'enfance. Par THÉRÈSE COMBY. Paris: Masson et Cie. 1935. Pp. 172. Price 30 francs.

The author's description is based upon a large series of personally observed cases of post-infective encephalitis and upon a review of the relevant literature.

The monograph is in the nature of a critical review of the subject, and will be found clear and comprehensive.

Les Hydrocéphalies Aiguës et Subaiguës d'origine Otique. Par R. BOURGEOIS. Paris: Masson et Cie, 1935. Pp. 178. Price 32 francs.

Under this title the author gives a comprehensive account, together with clinical summaries of all recorded cases, of the condition described in this country by Symonds under the name of "otitic hydrocephalus" (see this Journal, 1931, 54, 55). Otitic hydrocephalus is a rare complication of otitis media, usually of chronic otitis and in a young person. It is characterized by an acute onset and the appearance of the following signs: Papillœdema, a normal cerebrospinal fluid under increased pressure, headache and sickness. The author describes three forms, a diffuse cortical form, an encysted ventricular form and a form localized in the posterior fossa.

The symptomatology and differential diagnosis of these forms are discussed at length. Treatment by lumbar, cistern and ventricular punctures is described.

The monograph is a very comprehensive one, and will be of value both to otologists and to neurologists.

Die Welt der Geisteskranken. von K. BIRNBAUM. Berlin: Springer. 1935. S. 157. Price M. 4.80.

Most popular accounts of psychiatry revolt any psychiatrist who may look into them, and antagonize or mislead other intelligent readers. Professor Birnbaum's little book is an outstanding exception. With a command of the subject and a clarity of presentation that have made his scientific writings notable, he gives here an illuminating account of the natural history of sanity, touching more on the inner happenings than on the superficial phenomena. It is fresh in its mode of developing the theme, and informative even for psychiatrists. It would indeed be an excellent introduction to modern psychiatry for physicians, as well as for the larger public to whom it is addressed.

Emotions and Bodily Changes. A Survey of Literature on Psychosomatic Relationships. 1910-1933. By H. F. Dunbar. London: H. Milford, Oxford University Press. 1935. Pp. 595. Price 25s.

A reference book such as this is valuable in direct proportion to the conscientious labour expended on its compilation. Dr. Dunbar's labour has been prodigious. A classified bibliography, running to 2,251 titles and covering 125 large pages, is plain evidence of the pains she has taken in collecting the material, and 430 tightly packed pages of summarizing text enable the reader to save himself much effort. The notices do not aim at being critical or exhaustive, but it is possible from them to decide about consulting an original article, and to get an orientation in this confused field. The survey is in places incomplete but some selection was inevitable. The first part is devoted to problems of integration, psychophysiological mechanisms in disease, and measurement; under the last head the psychogalvanometer and biochemical methods are included, as well as some reference to the "Berger rhythm." The second, and major part of the text, deals with the different organ-systems in turn, and is followed by brief therapeutic considerations and some concluding remarks.

Pellagroide Dermatosen an Geisteskranken. By P. J. Reiter and J. Jakobsen. Kopenhagen: Levin and Munksgaard. 1935. Pp. 125.

Among nearly a thousand patients with mental illness in the St. Hans Hospital, Denmark, no less than a fifth were found to show dermatoses sufficiently like that of pellagra to raise the question of their nutritional origin. The authors consequently examined as controls a comparable number of convicts, who had lived in confinement for as long as the patients, and had been on a diet which was much poorer in vitamins and less varied than that given in the hospital. Among the convicts the number with pellagroid dermatoses was much smaller, and whereas there were fourteen insane patients with definite pellagra, at most only two of the convicts showed the disease. The cause for this difference was therefore assumed to lie in the patients rather than in their environment and diet. It was found that a majority of those with pellagroid dermatoses had either encephalitis lethargica or dementia præcox. In the encephalitics and some of the schizophrenics the dermatosis was attributed to disease of the central nervous system, especially in the hypothalamic region. In other schizophrenics, disturbances in absorption from the alimentary tract were held responsible for the appearance of true pellagra: this was in conformity with some earlier work on intestinal function by Dr. Reiter. It is difficult to account for so much higher a proportion of these dermatoses and of pellagra itself than could be found in similar English population: it may rest on different diagnostic criteria. In the cases reported, the pigmented hyperkeratotic plaques on the elbows and hands seem to have been given an excessive importance. The study is of interest in its bearing on the relationship between the skin and the mental state.

Mental Health; its Principles and Practice. By FRANK E. HOWARD and FREDERICK L. PATRY. New York and London: Harper Brothers. 1935. Pp. 551. Price 15s.

An elementary account of the psychobiology of Adolf Meyer is the groundwork of this rather verbose, but sound, manual of mental hygiene. The pedagogic side is given more prominence than in many books of the kind, and the mental health of children and adolescents is the chief theme, in accordance with the prophylactic aim evident in most of the chapters. The sensible, if somewhat conventional treatment, the simple mode of expression, and the guides to further reading and discussion at the end of each chapter, make this book a useful introduction to psychiatry in its broader constructive aspects.

Wach- und Wahrträumen bei Gesunden und Kranken. von Prof. F. KEHRER. Leipzig: Thieme. 1935. S. 72. Price M. 4.80.

The author properly remarks on the deficiencies of the literature bearing on the topic of day-dreams. It cannot, however, be said that his monograph supplies the lack. He gives a review of what others have written, from which some important American papers are omitted, and the only original material he offers consists of one case, with a pedigree, to which is appended the speculation about heredity now apparently de rigueur in German psychiatric writings. The study of day-dreaming in children and normal adults, which is so necessary for psychopathology, is inadequately covered, though there is a diffuse discussion of the fantasies of artists, poets and clairvoyants.

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EDITOR.

OCTOBER, 1936

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BRAIN.

PART 3, VOL. 59.

THE CLINICAL PICTURE OF MINOR CORD LESIONS IN ASSOCIATION WITH INJURIES OF THE CERVICAL SPINE: WITH SPECIAL REFERENCE TO THE DIAGNOSTIC AND LOCALIZING VALUE OF THE TENDON REFLEXES OF THE ARM (INVERSION OF THE RADIAL REFLEX).

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INTRODUCTION.
THE PRODUCTION OF THE VERTEBRAL INJURY.
THE CLINICAL PICTURE.
INVERSION OF THE RADIAL REFLEX (BABINSKI).
SUMMARY.
APPENDIX.
REFERENCES.

INTRODUCTION.

THE immediate consequences of a severe but non-fatal injury to the cervical spine and cord are so dramatic that they present no diagnostic difficulty. The quadriplegia with priapism and retention of urine which ensues upon such an injury has long been familiar to the clinician.

It is also known that an injury, fracture or fracture-dislocation, of the cervical spine may be sustained without any associated lesion of the spinal cord.

Between these two extremes are those cases with which we are now concerned, namely, those in which the spinal cord does sustain some relatively slight damage, either a momentary nipping when there is displacement of cervical vertebræ in relation to one another, or a momentary stretching over the posterior aspect of the vertebral bodies when the head is forcibly flexed, as in a fall in which the vertex strikes the ground first.

With the pathological changes produced in the cord in this way we are not here especially concerned. Indeed, no dogmatic statement can be made about them since the cases in question do not come to autopsy. But we believe that the clinical picture resulting from injuries of this less severe type has not been adequately described, is not uncommon, and is usually unrecognized.

Of the six cases which form the material of the present account, only one had been recognized, though more than one of them had been submitted to neurological examination. The diagnoses actually made included progressive muscular atrophy, amyotrophic lateral sclerosis, primary lateral sclerosis, and arthritis of the shoulder.

It has therefore seemed worth while to give a brief account of the clinical picture presented by these minor injuries of the cervical cord, since it is a recognizable picture, and when found in association with a history of injury leaves little room for error of diagnosis. Paradoxically, however, it is this history of injury which is in a measure responsible for directing attention away from the cervical spine and cord, since it is the head which first receives the violence and not the neck.

THE PRODUCTION OF THE VERTEBRAL INJURY.

In an analysis of spinal injuries, to which the reader is referred for details, Jefferson [4] has drawn attention to a number of points which are of importance in our present connection. He emphasizes that fractures and dislocations of the cervical spine are commonly produced by violence directed against the head. In other words, head injuries are the usual cause of injuries of the cervical spine. The original trauma may be trivial, but it acts by producing excessive flexion (anterior or lateral) of the cervical spine. In the majority of such cases the fracture or dislocation occurs between the 4th and 5th, or between the 5th and 6th vertebrae. The latter is probably the more common level.

All of the six cases which form the basis of the present account were cases of head injury primarily. All sustained scalp wounds, abrasions or contusions of the scalp. Four were rendered transiently unconscious, and the remaining two were transiently "dazed." In one case the patient was struck on the head by a motor car. One patient ran his head violently against a goal post while playing football. Three fell from small heights striking the head first on reaching the ground, and one slipped when entering a room, lurched and fell forwards, striking his head violently against a hot-water pipe near the floor level.

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Jefferson cites a typical case in which, as in these, attention was not unnaturally directed to the head injury. A bale fell from a height, felling a man who stood beneath it, rendering him unconscious and inflicting a scalp wound. When he recovered, the paralysis of his right arm which then became apparent was thought to be due to a contre-coup lesion of the left motor cortex. In fact he had sustained a fracture of the 5th cervical vertebra and an injury to the brachial plexus.

It is, then, clearly important in cases of head injury to bear in mind the possibility of damage to the cervical spine and cord, more especially if the patient subsequently complains of pain or stiffness in the neck.

THE CLINICAL PICTURE.

For the reasons mentioned, and also from the fact that in the type of case under consideration the paralysis of the limbs is not very severe or profoundly disabling, attention is usually not drawn immediately to the spinal or cord injury. If the patient happens to have been concussed and to have been confined to bed for some time, it may not be until he gets up and begins to resume activity that his attention is drawn to disabilities that he may not previously have noticed, or that he may have attributed to his general condition.

In some instances where consciousness has not been lost at the moment of injury, as in Case 2 in the Appendix, the patient complained at once of a "dead feeling" from the neck downwards, while another (Case 4 in Appendix) continued to complain of tingling in his hands, and of accesses of tingling running down his arms and legs if he bent his head forward. These symptoms he had noted from the moment of regaining consciousness after his fall.

In one case only out of the six was there any disturbance of sphincter control. This patient (Case 1 in Appendix) was incontinent of urine and fæces for some three weeks after his accident, but as he was mentally considerably reduced it is difficult to assess the significance of these disorders.

The common story given by the patients is that when the resumption of activity begins after recovery from the immediate effects (e.g. concussion) of the injury, they find the arms alone, or both arms and legs weak. This weakness may persist unchanged, may gradually and partially clear up, or may even slowly increase with the passage of time. In our experience, it cannot be assumed that the relatively moderate degree of the initial disability means that complete recovery may be looked for within a short or measurable period.

The appearance of muscular wasting in the upper limbs is not invariable, and when it occurs may not be noticed by the patient for some weeks, but in one case (Case 1) it was already marked when he came under observation in the third week after the injury.

Systematic examination of the nervous system reveals the following signs :—

Cervical sympathetic.—Slight narrowing of the palpebral fissures with relative smallness of the pupil was observed in one case. In the remaining five there were no signs of a lesion of the sympathetic pathway.

Motor system.—In one case there was wasting of the spinati, deltoid, biceps and triceps on both sides, with free fibrillation of these muscles. In another there was wasting of this distribution on one side. In the remaining cases no unequivocal wasting of local muscle groups could be seen. Tenderness of the wasted muscles was present. In the cases with wasting of the deltoid there was marked weakness of this muscle, but the disability was aggravated by the development of arthritis in the shoulder joint in both cases. This was probably largely due to lack of movement in the joint following the injury, and the rapidity with which in a hemiplegia, particularly a left hemiplegia, a similar condition develops in the shoulder joint is familiar to neurologists.

The forearm muscles showed slight hypertonus with slowness and clumsiness of fine movements: in other words the arms presented the combined signs of upper and lower motor neurone lesions.

In the legs slight hypertonus of extensors and plantarflexors, with a trace of weakness of dorsiflexion on one or both sides, or no weakness at all, are all that was found.

Sensory system.—Contrary to what might have been expected no objective sensory loss was found in five of the six cases. In the sixth (Case 3) there was a strip of impairment of sensory acuity to light touch and to pin-prick on the ulnar side of the left forearm. It must be borne in mind, however, that all but one of the cases came under our observation only after the lapse of weeks or months from the date of the injury. It is possible that in some at least, sensory changes had been present at the outset.

Pain in the neck and pain radiating down one or both arms was commonly complained of, and it was said by the patients to be more severe in wet and cold weather. As already mentioned, a tingling sensation radiating down the arms was also complained of.

Reflexes.—Perhaps the most significant diagnostic information was obtained from the study of the tendon reflexes of the arms. In the routine examination of cases of nervous disease relatively little interest is displayed in these, and the account given by Babinski of the form and meaning of what he has called "inversion of the radial reflex" [1, 2] is not as widely known as it should be.

Whereas in amyotrophic lateral sclerosis with which these cases of cervical cord injury are commonly confused, the tendon jerks of the arms are uniformly, and sometimes considerably, increased, in these traumatic cases the various tendon jerks of the arms are varyingly affected : some are increased, some diminished or abolished, and one—the supinator jerk—may be replaced by finger flexion (inversion of the radial reflex). Thus it is common to find the triceps jerks greatly increased, the biceps jerks normal or diminished, and the supinator jerk on one or both sides replaced as described.

It is this differential behaviour of the arm-jerks that indicates the presence of a focal lesion of the spinal cord in the region of the 5th cervical segment, the segment usually involved in this type of spinal injury.

In the lower limbs the knee and ankle jerks are commonly exaggerated and ankle clonus may be present on one or both sides. Extensor plantar responses were present bilaterally in four of the six cases. Both responses were flexor in the remaining two.

The abdominal reflexes were abolished on one side in one case (R. B.), but were intact in the remaining cases.

Gait.—All but one of the patients were able to walk unassisted, but some cases did so with a slightly spastic gait and the tendency to trip easily and fall heavily that such patients usually show. One patient (Case 1) had been confined to bed since his injury and had not yet got up when he was under our observation.

Sphincters.—The patient just mentioned had incontinence of urine while under observation. In the remaining cases there was at no time any disturbance of sphincter control.

The cervical spine.—In all the cases there was manifest limitation of rotation of the head, with complaint of pain when the limit was reached if the effort to turn further was sustained. The limitation was not always equally marked in rotation to the two sides. Some limitation of extension of the neck was also present. Lateral flexion was usually both painful and limited. Two of the patients held the head stiffly at all times and thrust slightly forwards.

In one case only did a radiogram give unequivocal evidence of displacement of vertebræ. In Case 4 there was clear narrowing of the intervertebral spaces between C 5, 6 and 7. In the others some degree of arthritis was present, but perhaps not more than was compatible with the age of the subject, for most of them were fifty years or over.

In short, the essential elements in the clinical picture are as follows: (*a*) Limitation of movement of the head and neck, with pain and stiffness on movement. (*b*) Some general weakness of the upper limbs, sometimes associated with special weakness and wasting of muscles supplied by the 5th and 6th cervical segments. Some hypertonus and slowness of movement may also be found. (*c*) Characteristic differential changes in the tendon-jerks in the arms, usually including inversion of the radial reflex. (*d*) Slight hypertonus of the extensor group in the legs, with increased knee and ankle jerks, and in some cases ankle clonus and extensor plantar responses. Slight weakness of dorsiflexion and a spastic gait may also be seen. (*e*) An absence of sensory loss, at least at the time at which the cases have come under our observation. There was a single exception to this generalization (Case 3). (*f*) Absence of defects of sphincter control. (*g*) Slow and imperfect recovery.

INVERSION OF THE RADIAL REFLEX (BABINSKI).

This phenomenon was described by Babinski in 1910 [2] as follows: " Nous avons dit que la percussion de l'extrémité inférieure du radius provoque toujours, à l'état normal, une flexion de l'avant-bras sur le bras. Celle-ci s'accompagne parfois d'une flexion de la main et des doigts: mais ce dernier mouvement, chez l'individu sain, a une intensité qui est généralement inférieure à celle de la flexion de l'avant-bras sur le bras et ne lui est jamais supérieure. Or, la diminution ou l'abolition du reflexe de flexion de l'avant-bras, état pathologique, peut avoir cette conséquence que la percussion de l'extrémité inférieure du radius détermine une flexion de la main et des doigts l'emportant en intensité sur la flexion de l'avant-bras ou se produisant alors que celle-ci fait défaut. C'est ce phénomène que j'ai décrit sous la dénomination d'*inversion du reflexe du radius* et dont la réalité a été confirmée depuis par de nombreux observateurs."

This lengthy statement is perhaps necessary since in the rare instances in which the phenomenon is mentioned in English textbooks, it is inaccurately described. In any circumstances in which there is a general increase in the arm-jerks, as in a residual hemiplegia, or in amyotrophic lateral sclerosis or disseminated sclerosis, it is not unusual to find that on eliciting the supinator-jerk, or even the biceps jerk, the appropriate response is accompanied by some reflex finger flexion. This is not inversion of the radial reflex, but it is so described in the textbooks in question and the term is thus deprived of any significance.

Discussing the localizing value of this inversion, Babinski ([1] p. 72) says that in lesions of the cervical region of the cord, the tendon-jerks of the lower limbs are uniformly increased, but that it is otherwise with the arm jerks the form of which depends upon the localization and length of the lesion. If it extend from the 5th to the 8th cervical segments all the arm-jerks may be abolished. With less extensive lesions not all the jerks may be abolished and inversion of the radial reflex may be seen. For this to occur three conditions are necessary: (i) there must be a lesion of the 5th cervical segment; (ii) the 8th cervical segment must be intact, (iii) there must be involvement of the pyramidal tract at a level higher than the 8th cervical segment.

As a rule, inversion of the radial reflex is accompanied by increase of the triceps jerk and by diminution of the pronator reflex (percussion on the front of the head of the radius, movement of pronation of wrist).

Pathologically, this phenomenon is most often seen in syringomyelia and in traumatic lesions and compression of the cervical cord.

Numerous examples of this inversion, with the verification of its segmental localizing value, are to be found in the pages of the *Revue Neurologique* during the period 1910-1915. Gendron has given a detailed account of this and other segmental signs in his *Thèse de Paris* [3].

We have, then, a clinical picture which is not that usually given as characteristic even of the slighter degrees of spinal cord injury. Thus, in the discussion on spinal injuries, Jefferson's contribution to which we have already cited, the account given by Riddoch [5] of the cord injuries is of a far graver type of injury than that we are now considering. The presence of sensory loss is assumed as constant, and the localizing indications obtainable from its upper level discussed. In short, this description gives no indication of the existence of the clinical type under discussion, and in so far as it purports to cover the ground of spinal cord injuries from cervical fracture and dislocation might almost be taken to exclude the occurrence of milder types than it describes.

It will be seen that there are many factors which militate against the recognition of these mildest forms of cord injury. The causative injury is ostensibly one of the head, the spinal cord symptoms may come to notice only after an interval; when seen they are not of the kind usually associated with injury: that is, they lack sensory loss and sphincter disturbance amongst their number. For this last reason they are very apt to be diagnosed as indicating early amyotrophic lateral sclerosis, and the history of trauma is lightly swept aside as irrelevant.

It is in these circumstances that the careful examination of the tendon reflexes in the upper limbs becomes so important; is, in fact, the basis of an accurate diagnosis.

Further, these reflexes serve also to differentiate pure nerve root or plexus lesions from cord lesions. If the weakness and wasting corresponds to a lesion of the upper roots of the plexus, the presence of bilateral changes in the arm-jerks points to a lesion of the 5th cervical segment, either as the sole or as an associated lesion.

SUMMARY.

A brief account is given of the clinical picture of a relatively slight type of damage to the cervical cord associated with dislocation or fracture of the cervical spine. In this the initial disability is comparatively slight and there is neither sensory loss nor impairment of sphincter control. The original violence which causes the spinal injury is always applied to the head, and thus attention is easily diverted from the presence and nature of the essential lesion.

The condition is commonly diagnosed as amyotrophic lateral sclerosis, progressive muscular atrophy or primary lateral sclerosis, owing to the absence of sensory changes and of disturbances of bladder control. *The most important and most characteristic feature in the clinical picture is the differential behaviour of the tendon-jerks in the arms, and the common—though not invariable—presence of inversion of the radial reflex.* As Babinski has shown, this phenomenon indicates the presence of a focal lesion in the 5th cervical segment of the cord. It is seen in compression of the cervical cord, in syringomyelia and in the type of injury to the cervical cord now under consideration. It is not seen in system degenerations of the cord, in which the tendon-jerks in the arms tend to be uniformly affected.

An additional feature of the clinical picture is the presence of some limitation of movements of the head and neck (anterior and lateral flexion and rotation). In only one of the present series of cases did radiographic examination of the cervical spine reveal a dislocation, but this negative finding is not unusual in severe and unequivocal cases of cervical spine dislocation with grave paraplegia. A normal skiagram does not, therefore, invalidate the diagnosis of injury.

Some authorities believe that amyotrophic lateral sclerosis may be traumatic in origin, but in view of the condition we have described it is permissible to wonder what proportion of cases so diagnosed are, in fact, cases of true amyotrophic lateral sclerosis.

In the Appendix six illustrative cases are described.

APPENDIX.

Case 1.—R. B., farm labourer, aged 65. (U.C.H., 1936.)

History.—Fell from the top of a hay cart to the ground, striking the left side of his head and his left shoulder. Was dazed, but did not lose consciousness. Complained at once of loss of power in both arms. Taken to local hospital and found to be weak in all four limbs. While in this hospital he was incontinent of urine and fæces.

Examination (twelve days later).—Patient is confused mentally and a bad witness (has previously been an inmate of a mental hospital). He complains of pain in his neck and radiating down both his arms. Cranial nerves and cervical sympathetic normal.

Upper limbs.—There is profound weakness of the left arm, especially of deltoid, triceps and biceps. He cannot raise the arm off the bed, and the grasp is feeble. The right arm and the left forearm show some slight general wasting. There is moderate weakness of the right arm in all movements. The deltoid, triceps and biceps fibrillate freely on both sides. The dorsum of the left hand is œdematous.

Lower limbs.—No wasting, slight weakness of dorsiflexion, general extensor hypertonus of slight degree in both legs.

Sensory.—No trace of sensory impairment for any form of sensation can be detected on trunk or limbs. No complaint of paræsthesiæ in arms or hands.

Reflexes.—Jaw jerk absent.

	R.	*L.*
Biceps jerk.	Diminished.	Diminished.
Triceps jerk.	Increased.	Increased.
Supinator jerk.	Absent (replaced by finger flexion).	Diminished (with brisk finger flexion).
Knee jerk.	Brisk.	Brisk.
Ankle jerk.	Brisk.	Brisk.
Abdominal reflexes.	Normal.	Diminished.
Plantar responses.	Extensor.	Extensor.

During the three weeks this man remained under observation, he was kept in bed, as he was generally feeble, demented and dirty. Whether his incontinence could be related to his spinal injury or not is uncertain.

An X-ray of his cervical spine revealed the presence of arthritis but no sign of injury.

The case is included, although the injury was more severe than the others of the series, because although seen within two weeks of a manifestly fairly severe cord lesion, there was no sensory loss.

Case 2.—J. H., a carpenter, aged 61.

History.—Had always enjoyed good health. For some years had ridden 12 miles daily on his cycle to and from work.

In January, 1932, when entering a room, he slipped, lurched forwards and fell, striking his head violently against a hot water pipe which ran round the room about a foot from the floor. For a few moments he lay on the floor, dazed and feeling "dead from the neck down." He was helped to his feet, and taken for first aid treatment to the local hospital. Remained there overnight and then went home by bus.

Two days later he returned to work, travelling by bus. His legs felt dead and he could not guide them properly. His arms were weak and clumsy, and from the day of the accident he had been unable to mount or to ride his cycle. He could walk slowly and laboriously.

General examination.—The patient held his head stiffly when standing and walking. The range of rotation, flexion, extension and lateral flexion was restricted—that of rotation most severely. Optic discs and cranial nerves were all normal. Jaw jerk was absent.

Upper limbs.—Slow and clumsy in all movements. Power diminished in all movements. Could not elevate either arm to the vertical. Hand movements particularly clumsy. Isolated movements of the digits lost. No localized muscular wasting, but arms thin throughout.

Lower limbs.—Slight hypertonus of the extensors, but no definite weakness.

Sensory system.—No trace of loss or impairment of any mode of sensation in limbs or trunk.

Reflexes.—Jaw jerk absent.

Biceps. Supinator.	*R.* Both absent and replaced by finger flexion.	*L.* Both normal.
Triceps.	Increased.	Increased.
Knee.	Increased.	Increased.
Ankle.	Increased.	Increased.
	(Transient clonus on both sides.)	
Abdominal.	Feebly present on both sides.	
Plantar responses.	Extensor on both sides.	

Gait.—Spastic and laboured.

Radiogram of spine.—Arthritis, no sign of injury.

Case 3.—M. A., a nurse, aged 50. (U.C.H., 1936.)

History.—Knocked down by motor car while dismounting from a tram. Unconscious, regaining consciousness in hospital in an hour or so. Had a bruise on forehead and another on the point of the left shoulder. The left side of the head was tender for some days.

Since the accident has complained of pains in the neck, aggravated by any rotation of the head. Pain radiating down both arms, and numbness on the inner side of the left forearm and hand.

Many symptoms of a traumatic neurosis developed in the ensuing weeks, e.g. fear of traffic, sleeplessness, depression, nervousness, &c.

Examination (four months later).—Cranial nerves and cervical sympathetic normal.

Upper limbs.—Very slight wasting of the interossei of the left hand, with some tenderness of these muscles and weakness of movements employing them. This weakness was but slight, and in other respects the arms were normal.

Lower limbs.—No abnormality.

Sensory system.—Slight blunting of acuity to cotton-wool touch and to pinprick on the ulnar side of the left forearm, and just extending on to the hypothenar eminence.

Reflexes.—Jaw jerk absent.

Coracoid reflex (i.e. percussion over coracoid)	*R.* Brisk, general flexion of arm.	*L.* Diminished.
Biceps.	Brisk.	Normal.
Triceps.	Very brisk.	Very brisk.
Supinator.	Very brisk (no finger flexion).	Normal (with brisk finger flexion).
Knee.	Brisk.	Brisk.
Ankle.	Brisk.	Brisk.
Abdominal.	Normal.	Normal.
Plantars.	Flexor.	Flexor.

Gait.—Normal. *Cervical spine.*—Movements limited and painful.

In this case the change in the left supinator jerk, which was verified by examination upon a later occasion, provided the only wholly unequivocal sign in a patient whose neurotic state rendered the assessment of her motor and sensory signs difficult.

Case 4.—J. E., engineer, aged 52. (U.C.H., 1936.)

History.—Fell from a step-ladder when standing 6 feet above ground level, striking the top of his bald head on the edge of an open furnace door. Was unconscious for some minutes. Sustained a long scalp wound, sagittally across the vertex. The wound was stitched and healed well. Since the accident he has had almost constant "nagging" pain in the neck and the back of the head. This pain runs down both arms, and in addition his hands feel as though he was "holding the terminals of a battery." This tingling sensation is worse whenever he bends his head forwards, and persists undiminished six months after the accident.

Both arms feel weak, but the left arm and hand are much weaker and more painful than the right. The weakness seems to have increased and now he cannot lift the left arm above the shoulder, and the effort to do so provokes severe pain in the shoulder.

Of his legs he makes no complaint, and he has been up all day and on his feet since his scalp wound healed.

General examination.—Long healed and pigmented scar of scalp wound. Rotation and flexion (anterior and lateral) of neck is markedly limited in range, especially rotation of the head to the left, and effort to exceed the range is painful. Active and passive movement of the left shoulder is greatly limited and there are clearly adhesions in the joint.

Cranial nerves and cervical sympathetic normal.

Upper limbs.—There is marked wasting of the left deltoid, and the left upper arm is three-quarters of an inch less in circumference than the right. The spinati are also slightly wasted. All movements of the limbs are of less than normal power, and the deltoid is not only wasted but is very weak. The right arm is thin, but shows no local muscular wasting. There is no fibrillation in either arm.

Lower limbs.—No abnormality. Walks normally.

Sensory.—No objective impairment of sensation on trunk or limbs.

Reflexes.—Jaw jerk absent.

	L.	*R.*
Biceps.	Diminished.	Normal.
Triceps.	Diminished.	Normal.
Supinator.	Diminished (finger flexion brisk).	Normal.
Knee.	Normal.	Normal.
Ankle.	Normal.	Normal.
Abdominal.	Sluggish.	Sluggish.
Plantars.	Flexor.	Flexor.

Wassermann reaction negative in blood and cerebrospinal fluid.

X-ray.—Marked narrowing of intervertebral space between C. 5, 6, 7.

Case 5.—T. S., a labourer, aged 33. (U.C.H., 1936.)

History.—Ran heavily against a goal post while playing football, striking his head. He fell momentarily unconscious, as he believes. On coming round, he had to be helped to his feet and was just able to walk, when supported on both sides, to an adjacent seat. Was taken home by car. Was then assisted to hospital, feeling "numb from the waist down" and as though his feet were too large for him. Was discharged from hospital after five days, and was then able to walk alone, but not with normal strength. Since resuming activity, he has found that whenever he bends his head forwards a feeling "like an electric shock" runs down the back of his legs and down his arms. He now feels perfectly strong again, apart from a feeling of stiffness in the left arm.

Examination (five months later).—Slight limitation of rotation of head, with a little pain at the limit of movement. Flexion of the head forwards provokes the "electric shock" feeling mentioned above.

Cranial nerves and cervical sympathetic normal.

Upper limbs.—Doubtful wasting of left deltoid, and suggestion of stiffness in movements of the left arm, but no weakness of either arm. No fibrillation.

Lower limbs.—No abnormality, walks normally.

Sensory.—No abnormality.

Reflexes.—Biceps.	*R.* Brisk.	*L.* Brisk.
Triceps.	Very brisk.	Very brisk.
Supinator.	Brisk.	Brisk.

(Both with extremely brisk finger flexion.)

Knee and ankle jerks normal on both sides.

Abdominal reflexes normal on both sides.

Plantar responses normal on both sides.

Wassermann reaction negative in both blood and cerebrospinal fluid. The latter being normal in all respects.

X-ray of cervical spine: nil abnormal.

In this case, a slight, but constantly observed, abnormality in the arm jerks is all that remains.

Case 6.—M. D., a married woman, aged 62. (1935.)

History.—Was knocked down by a car when crossing the street. Was unconscious until next day. Scalp wound on forehead, damage to nose and bruises on the right shoulder. Remained confused for some days, and was in bed in hospital for a month.

When she began to get up and to move about she found that she could not lift her arms properly, could not reach her head to brush her hair, the neck was very stiff and ached constantly. Aching pains ran down both arms, which slowly began to get thinner. Her legs also were stiff and walking was a labour. It took her over an hour to dress in the morning. At times, if she gets tired, both legs drag. At the time of coming under observation, the diagnosis was one of traumatic neurasthenia following a head injury.

On examination (six months after injury).—The head is held very stiffly, and rotation and anterior flexion are painful and very limited in range. She has to turn her whole body when she wishes to look to one side. The pupils are small, the palpebral fissures narrow, especially on the left side.

Upper limbs.—There is general weakness, slight general wasting, and slight hypertonus of both arms. Deltoids are specially weak, and she cannot elevate either arm to the vertical. All movements except this are possible, but are slow and a little clumsy. There is a suggestion of local wasting of the small hand muscles.

Lower limbs.—Slight general spasticity, slight weakness of dorsiflexion of both feet, with a tendency to drag the toes when walking.

Sensory.—No impairment of any form of sensation on trunk or limbs.

Reflexes.—Jaw jerk absent.

Biceps Triceps }	*R.* Very brisk.	*L.* Very brisk.
Supinator.	Normal. (Accompanied by brisk finger flexion on both sides.)	Normal.
Knee.	Very brisk.	Very brisk.
Ankle.	Very brisk. (Transient clonus.)	Very brisk.
Abdominal.	Present.	Present.
Plantar.	Extensor.	Flexor.

X-ray of cervical spine reveals severe arthritis.

During the eighteen months that this patient remained under periodical observation, she made a slow and imperfect recovery. The reflexes remained unchanged. Walking improved slightly, and the range of movement at the shoulders improved. The wasting of the small hand muscles appeared to increase for a few months, but finally became stationary.

REFERENCES.

[1] BABINSKI, J. "Œuvre Scientifique (Receuil des principaux travaux)." Masson et Cie., Paris, 1934. Pp. 51 and 72.
[2] *Idem.* *Bull. et Mém. de la Soc. des Hôp. de Paris*, 1910, **30**, 185.
[3] GENDRON, A. *Thèse de Paris*, No. 229, 1918. Maloine et Cie., Paris.
[4] JEFFERSON, G. *Proc. Roy. Soc. Med.* (Sect. of Orthopædics), 1928, **21**, 21.
[5] RIDDOCH, G. *Ibid.*, 1928, **21**, 33.

TUMOURS INVOLVING THE VENTRAL ASPECT OF THE PONS AND MEDULLA, INCLUDING TWO CHORDOMAS.[1]

BY LEWIS D. STEVENSON, M.D., AND E. D. FRIEDMAN, M.D. (NEW YORK).

INTRODUCTION.

Two cases of tumour at the base of the brain were observed in the Neurological Service at Bellevue Hospital, a third was studied by one of us (L. D. S.) at New York Hospital, and the fourth occurred in private practice. All of the cases presented similar clinical signs and symptoms. The two cases observed at Bellevue Hospital had been diagnosed as possible tumours of the fourth ventricle. Two of the tumours described are of further interest because of the pathological findings. They were cases of chordoma, a tumour derived from the remains of the notochord.

CASE REPORTS.

Case 1.—F. W., aged 33, housewife, was admitted to Bellevue Hospital on April 25, 1927. Her chief complaints were headache, blurring of vision, and pain in the back of the neck of two years' duration.

Previous history.—At the age of 14 the patient suffered from poliomyelitis, which left considerable weakness of the left lower extremity. Menstrual history was normal. There was an internal strabismus of the left eye, dating back to early life.

Present illness.—In December, 1924, the patient complained of numbness of the tongue, a feeling of pressure in the eyes, and blurring of vision. A year later she suffered from a dull " aching pain " over the vertex: she was operated upon for " sinusitis," but did not obtain relief. The headache continued. It was paroxysmal in type, began at the base of the skull, radiated forward and led to retraction of the head. Occasionally it was accompanied by vomiting. There were also periodic attacks of numbness of the tongue. One week prior to admission the patient suddenly lost consciousness. During the episode there was conjugate deviation of the eyes to one side, but no convulsion. In the latter part of 1926 and early in 1927 she suffered from outbursts of uncontrollable laughing. In February and March, 1927, she also complained of drowsiness.

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[1] From the Neurological Service, Neuropathological Laboratory of Bellevue Hospital, and Department of Neurology of New York University, College of Medicine.

Case reports presented in part before the Section of Neurology and Psychiatry of the New York Academy of Medicine, October 11, 1932.

General medical state showed no abnormalities. Blood-pressure readings were 115/85.

Neural status.—There was bilateral papillœdema with hæmorrhages. Visual fields were normal. The pupils were normal. Palsy (old) of the left external rectus was found; no true nystagmus, but a few vertical jerks of the eyeballs upward. Right facial weakness and diminution of the corneal reflexes, especially the left, were noted. The lower jaw deviated to the left and there was a mild left-sided nerve deafness. Palate innervation was impaired, especially on the right, and the gag reflex was lost. Innervation of the larynx was normal, and labyrinthine tests yielded normal responses.

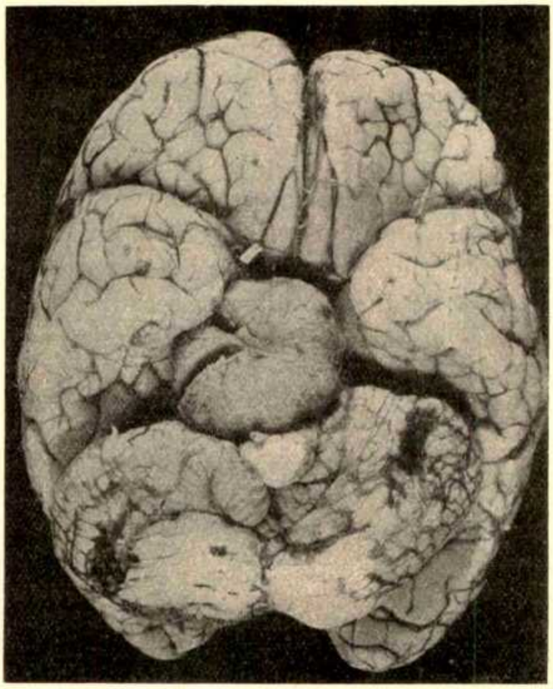

FIG. 1.—Showing the tumour in Case 1. It measured 3·5 c.m. in diameter and was firmly adherent to the dura over the basilar portion of the occipital bone, just behind the sella. It is compressing the pons and the basilar artery, being attached firmly to the pons, more on the right side than the left. The tumour also compressed the Aqueduct of Sylvius, resulting in internal hydrocephalus and giving rise to papillœdema and headache. There was some compression and rotation of the medulla. The radiating streaks of an endothelioma can be seen in this figure. Microscopically it was a typical endothelioma of the meninges, with psammoma bodies in it.

There was weakness in the right grip and in the movements of both lower extremities, with atrophy of the peroneal and flexor groups, more pronounced on the left (poliomyelitic residua). The deep reflexes were more active on the right. The left Achilles jerk was absent. Abdominals were not obtained. The plantars were equivocal but Babinski's sign could not be elicited.

Sensation was intact in all forms. There was ataxia in the finger-to-nose test on the right. Gait was somewhat unsteady; there was a tendency to veer from side to side, more so to the right. Mental status showed no abnormalities.

X-ray examination of the skull proved negative. Blood chemistry figures and urine were normal.

The clinical impression was that of a neoplasm in the posterior fossa, involving the medulla and 4th ventricle.

Sub-occipital exploration with removal of part of the foramen magnum was carried out on May 3, 1927. The ventricles were aspirated and 60 c.c. of clear fluid under pressure was removed. The cerebellum was tense on both sides. There was very great thickening of the meninges. The cerebellar tonsils were jammed through the foramen magnum. No evidence of tumour could be found in the 4th ventricle. The surgeon concluded that we were probably dealing with a neoplasm in the medulla.

Patient died suddenly on May 7, 1927.

Post-mortem examination revealed a meningioma at the base of the brain (see fig. 1).

Comment.—The duration of symptoms in this case was about two years; headache and pain in the back of the neck were quite prominent features of the illness. The numbness of the tongue may well have been due to interference with one or both 5th nerves as they enter the pons, although the signs of 5th nerve involvement were slight. There was no nystagmus or evidence of serious involvement of the cerebellum. There was slight weakness in the legs and in the right grip (superimposed on the original poliomyelitic residua), but the Babinski sign was not present. It is conceivable that the sudden loss of consciousness, once recorded, might have been due to interference with the blood-supply of the brain through pressure on the basilar artery, although it might easily have been due to other factors. Apart from the very slight evidence of pyramidal tract involvement, there were few signs of pressure on long tracts; there was no loss of sensation over the arms, trunk or legs.

Case 2.—Emily M., aged 31, housewife, was admitted to Bellevue Hospital, February 2, 1932.

Her chief complaints were tinnitus, dizziness, unsteadiness in walking, and throbbing pain in the right occipital region for six months; pain in the right temporal region for five months.

Present illness.—For two months prior to admission the patient suffered from generalized headache, particularly severe in the frontal zone. For three weeks, there had been spells of vomiting preceded by nausea and accompanied by frontal headache. Diplopia came on at about the same time. At first it was only transitory, later constant. She also complained of roaring in the ears, worse when she stooped forward, and more pronounced on the right. There was some impairment of hearing for four or five weeks preceding admission.

Neural status.—There was bilateral early papillœdema. Visual fields showed no abnormalities. Pupils were normal. No true nystagmus was found, but occasional vertical jerks upward. Weakness of the right 6th, impairment of bone conduction on the right, and absence of the gag reflex were noted. Bárány tests gave normal responses. The patient showed a tendency to fall backward and to the right, cerebellar ataxia on the right side, generalized increase of deep reflexes, and absence of abdominal reflexes. There was tenderness of the right occiput.

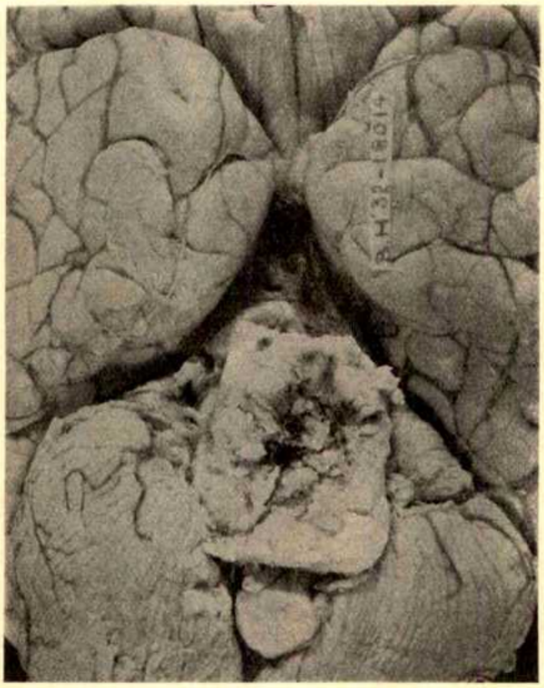

FIG. 2.—Showing the tumour of Case 2. It was 4·5 cm. long, 3 cm. wide, and 1·5 cm. deep. It was attached to the anterior surface of the pons and medulla in the middle line, but was somewhat thicker on the right side than on the left. It felt like soft rubber with spicules of bone over its surface. Sections of this tumour showed it to be a chordoma, and sections of the eroded bones of the skull underneath it showed chordoma cells in abundance.

She held her head in a fixed position, somewhat forward ("ceremonial attitude") and resisted anterior flexion. On two occasions she experienced difficulty in swallowing. The tongue felt stiff in its posterior part, and at times the patient found difficulty in speaking. When she voluntarily turned her head to the right, she experienced pain in the right occipito-cervical region.

The serological findings were negative, and X-ray examination of the skull showed no abnormalities except for a somewhat closed-in sella.

PLATE II.

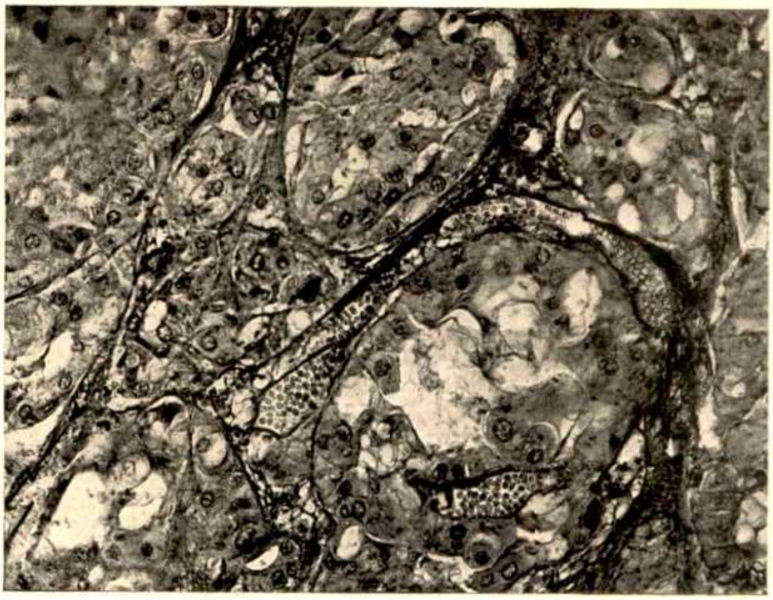

FIG. 3.—Showing the general microscopic appearance of the tumour with the cells separated by strands of connective tissue containing mucin and also denser fibrous tissue which stained pink with van Gieson's stain. The cells are large and contain many vacuoles or bubbles within their cytoplasm, and many contain more than one nucleus. The cells are, as a rule, not well defined individually in our sections, but form a sort of syncitial network which is well illustrated in fig. 4.

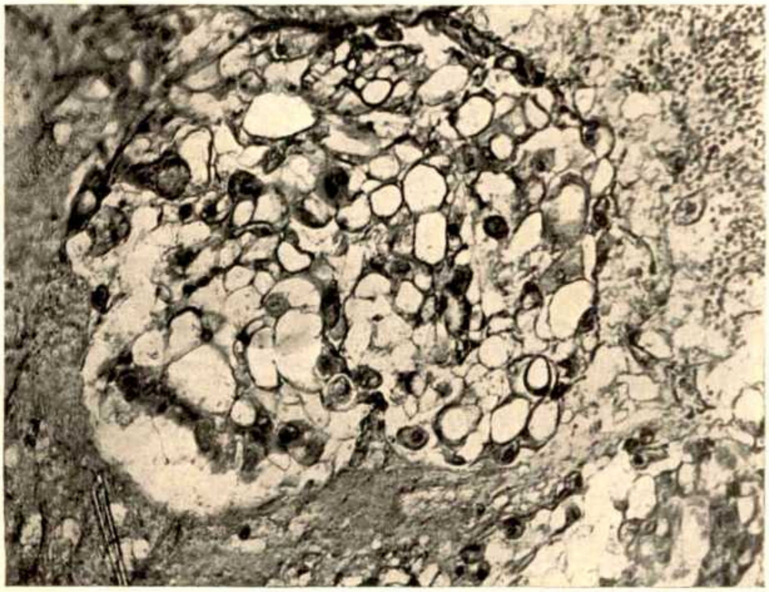

FIG. 4.—This figure also demonstrated the physaliphorous cells of chordomas. The bubbles or apparent vacuoles of those cells are said to contain mucin, although some pathologists have thought they were filled with glycogen. These physaliphorous cells are characteristic of this tumour, and are not found in degenerating cartilaginous tumours which are sometimes confused with chordomas.

To illustrate paper by Lewis D. Stevenson and E. D. Friedman.

On one occasion the patient volunteered the statement that when she turned toward the right she experienced peculiar movements in the tongue. These were accompanied by paræsthesiæ, especially at the tip. This symptom disappeared abruptly when she shifted her position. These "hypoglossal fits" recurred from time to time.

Throughout the patient's stay in the hospital her chief complaints were intense pain behind the right ear and dizziness induced by bending forward suddenly (modified von Bruns' sign).

The clinical diagnosis was tumour of the posterior fossa.

Sub-occipital exploration, first stage, was carried out first. Later, the second stage was performed. Ventricular puncture yielded fluid under great pressure. After exposure of the cerebellum, there was found an adhesive arachnoiditis at the base with loculation of fluid. The arachnoid was definitely thickened but the tumour was not found.

Owing to increasing stupor, and in order to exclude a lesion further forward with invasion of the mid-brain, ventriculography was carried out. It showed distended lateral ventricles and a globular 3rd ventricle. Because of the absence of quadrigeminal plate phenomena, this was considered confirmatory evidence of a lesion in the posterior fossa. Following this procedure, the patient showed horizontal and vertical nystagmus, paralysis of the right 6th nerve, weakness of the left, right facial weakness, and protrusion of the tongue to the right (without atrophy). Re-exploration of the posterior fossa with splitting of the vermis was then suggested and carried out. At this time there was found an accumulation of fluid in the midline within a cavity lined by a membrane. The aqueduct of Sylvius was found patent. No evidence of neoplasm was found.

Repeated ventricular taps were carried out for symptomatic relief (130 to 160 c.c. of fluid was withdrawn).

Patient died on June 11. Post-mortem examination revealed a growth lying on the ventral aspect of the pons and the medulla and attached to the clivus (see figs. 2, 3 and 4). It proved to be a chordoma.

Comment.—This patient presented symptoms for six months only, although the tumour had probably been there for a much longer period. There was only slight internal hydrocephalus in this case. The basilar artery was greatly compressed by the growth. The 5th nerve was not involved on either side, but both 6th and both 12th nerves were compressed by the tumour. The pressure on the 12th nerve probably accounted for the peculiar movements of the tongue when the patient turned on her right side.

Case 3.—M. Q., aged 31, housewife (from New York Hospital, service of Dr. George J. Heuer, to whom we wish to express our indebtedness for permission to report the case).

Her chief complaints were dull occipital headache, fairly constant, but with occasional exacerbations, dizzy spells, vomiting, blurred vision, spots before the eyes, and staggering to the right on walking. These symptoms had been present for three months; they appeared after the delivery of a normal full-term child.

Examination showed an obese woman with tenderness in the occipital region and pain in the neck on flexion of the head. The patient was drowsy but normal mentally. Her vision was blurred and there was papillœdema with retinal hæmorrhages on both sides. Weakness of the right 6th nerve, with periodic diplopia, and a well-sustained lateral nystagmus, more pronounced to the right, were found. A clockwise type of nystagmus was present on looking upward and a counter-clockwise type on looking downward. Diminution of the right corneal reflex, hypoæsthesia and hypalgesia over the first and second divisions of the right 5th nerve were noted. Facial weakness, probably peripheral in type, was also present on the right side. Neither tinnitus nor deafness was complained of, and no deafness was demonstrated. Caloric tests gave normal responses on both sides. Speech was somewhat thick (dysarthria). The tongue was protruded to the right; showed no atrophy but some tremor.

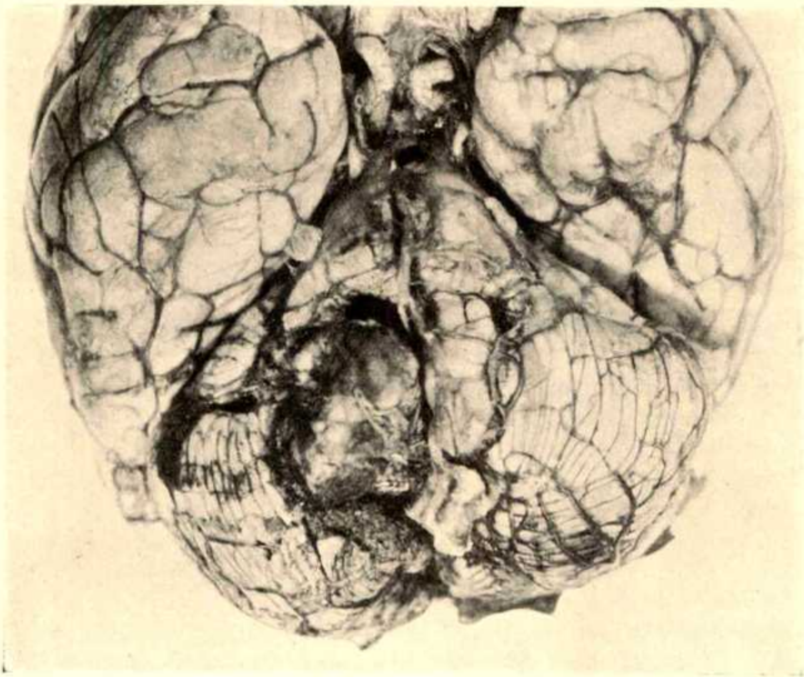

FIG. 5.—Showing the gross appearance and situation of the tumour in Case 3.

The diagnosis of a right cerebellar neoplasm was made. Exploration was carried out on October 4, 1932, by Dr. George J. Heuer. A large nodular tumour was found close to the lateral recess on the right, dislocating the brain-stem to the left. The patient did poorly, vomited dark coffee ground material, collapsed and died.[1]

Post-mortem examination revealed a tumour at the base of the brain on the right. There was a moderate degree of internal hydrocephalus with considerable hydrops of the 3rd ventricle. Sections of the tumour showed it to be a meningioma and the bone, removed from the region of the foramen magnum underneath the tumour, had been invaded by endothelial cells. The pituitary gland was somewhat enlarged, but not otherwise abnormal. The 7th and 8th cranial nerves on the right were very definitely compressed by the tumour. The 9th and 10th were apparently destroyed. The 5th nerve was not directly implicated on either side, but 5th nerve signs on the right may have been due to traction on this nerve when the brain-stem was distorted or dislocated to the left (fig. 5).

Comment.—The findings were those of a lesion at the base of the brain on the right with implication of the lower cranial nerves and the homolateral cerebellar pathways. The clinical syndrome was not that of an angle lesion.

Case 4.—This case is of interest because it could not be diagnosed in its earlier stages and because it also proved to be a chordoma. Further, the first and most outstanding feature of the case was a bilateral hypoglossal lesion with marked atrophy of the tongue; there were none of the classical signs of cerebral tumour.

A. W. P., a man, aged 59, was referred by Dr. Leander Shearer to one of us, (L. D. S.) because of dysarthria and difficulty in swallowing, noted first about August, 1931. This difficulty slowly increased and was later associated with pain in the back of the neck and in the occipital region.

Neurological examination in February, 1932, revealed atrophy of the tongue, more pronounced on the right side. There were no signs of pyramidal tract involvement, loss of sensation, choking of the discs or other signs of tumour within the skull. A diagnosis of bulbar palsy was made.

In May, 1932, the patient developed diplopia due to weakness of the left 6th nerve. Later, neurological examination revealed, in addition to weakness of the left 6th nerve, implication of the 10th and 11th cranial nerves, and the bilateral hypoglossal palsy already noted. There still was no evidence of pyramidal tract involvement or choking of the discs.

The patient was then lost sight of and died in another city in January, 1933.

Post-mortem examination revealed a tumour outside the dura at the base of the skull, invading the central part of the sphenoid bone and extending down through the base of the skull into the region of the posterior superior pharyngeal space. X-ray examination of the skull before the patient's death showed slight evidence of the presence of this growth. The tumour proved to be a chordoma.

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[1] This may have come from an ulcerative lesion of the gastric mucous membrane, similar to the ulcerations described by Cushing, following lesion of a pathway leading from the mid-brain to the brain-stem and supplying trophic filaments to the gastric mucosa.

DISCUSSION AND DIFFERENTIAL DIAGNOSIS.

The number of chordomas reported in the literature is about sixty. These neoplasms may grow from either end of the remains of the notochord. About an equal number from the region of the spheno-occipital synchondrosis and from the sacro-coccygeal region have been described. Only a few involving the cervical, lumbar and thoracic regions of the spine have been reported. These growths are usually not malignant, but if removed surgically tend to recur. Occasionally they give rise to metastases in other parts of the body. Ribbert, in 1894, produced these tumours experimentally by puncture of the intervertebral cartilages in animals. He suggested the name chordoma because he demonstrated that these growths were derived from the vestigial notochord.

A case reported by D. F. Cappell of Glasgow in 1928 showed, in places, the structure of the primitive notochord with primary and secondary sheaths surrounding the physaliphorous cells, thus adding the final proof that these tumours are actually derived from the notochord.

Chordomas occur more frequently in males than in females, and are found from the age of 16 up to 51 years or more.

One cannot establish a definite syndrome for tumours located in this region, but we believe now that signs of involvement of one or both hypoglossal nerves, or others of the lower cranial nerves, might help to place the tumour in front of the pons and medulla rather than in the 4th ventricle. Moreover, these tumours differ in several important respects from tumours invading the pons (e.g. glioma), from acoustic neuromas, and from tumours of the 4th ventricle.

Tumours of the 4th ventricle itself usually give rise to the von Bruns' sign (sudden vertigo with change in posture), signs of internal hydrocephalus with perhaps evidence of distant pressure on the chiasm owing to herniation of the floor of the 3rd ventricle. These cases, as a rule, are characterized by the absence of cranial nerve phenomena. The posture of the head frequently found in such instances is not always of the same type. We have encountered cases of tumour of the 4th ventricle which gave rise to forward displacement and flexion of the head in the typical "ceremonial attitude." One of us has observed this type of attitudinizing and fixation of the head in a case of teratoma overlying the 4th ventricle (subsequently reported by Klenke and Brock). In other instances of similar localization there has been retraction and over-extension of the head with a tendency to the assumption of the attitude of decerebrate rigidity. We have recently had occasion to observe a case of ependymoma of the 4th ventricle with such retraction and over-extension of the head. One might say that, in general, posturing of the head is highly suggestive of a lesion in the posterior fossa, although we have on rare occasions encountered this symptom in cases of supratentorial growths. In cases of tumour involving the cerebello-pontine angle, the head is frequently tilted to one side with the chin directed towards the site of the lesion.

As has already been stated, there is no symptom complex characteristic of tumours at the base of the brain. Selinsky recently reported an instance of chordoma, somewhat further forward in localization than our own cases, in which optic atrophy, multiple ocular palsies, and erosion of the sella were found.

In a retrospective survey of our cases, one might say that the diagnosis of a ventrally-placed lesion is not easily made. The " hypoglossal fits " in one of our cases were, of course, exceedingly suggestive. Since the advent of careful encephalographic studies of the subarachnoid spaces, one would look for evidence of encroachment on the cisterna pontis. In the main, one would have to be content with a diagnosis of a lesion of the posterior fossa, and if the surgeon, on exploration, failed to find the lesion dorsally placed, it would be a prudent measure to explore the ventral aspect of the brain-stem for evidence of the growth. The surgical removal of these ventrally-placed neoplasms is, of course, not an easy matter.

Many of these tumours at the base are latent and symptomless, but they may involve any of the lower cranial nerves from the 8th to the 12th. They are frequently accompanied by disturbances in respiration and heart-rate, and the presence of intermittent glycosuria (phenomena due to the invasion of or contrecoup pressure against the 4th ventricle). Some of the more characteristic signs and symptoms include occipital headache, attitudinizing of the head, cerebellar ataxia, and an intermittent course.

The paræsthesia of the tongue described in one of our cases may have been due to stretching of the 5th nerve. The condition of the bone at the foramen magnum in Cases 2 and 3 might have given us a clue as to the localization, if careful radiographic studies of this region had been made, as was done in Case 4.

Ependymomas of the 4th ventricle are more apt to give rise to pain on turning the head, due to extension of the growth either upward from the spinal cord or downward from the 4th ventricle. This advance through the foramen magnum results in increase of the size of the brain-stem with tension on the meninges or the vessels.

Lesions of the cerebello-pontine angle are readily excluded by the presence of signs and symptoms referable to both divisions of the 8th nerve, characteristic nystagmus with the coarse component directed towards the side of the lesion, areflexia of the cornea and homolateral cerebellar signs. Vestibular tests on the side of the neuroma show definite impairment of function, sometimes even before deafness is noted.

Syphilitic meningitis at the base might enter into the differential diagnosis, but it is more apt to give rise to the picture of an angle lesion [2].

Atypical multiple sclerosis would be characterized by active remissions and exacerbations, more definite implication of the pyramidal tracts and posterior columns, and phenomena referable to the upper cranial nerves, especially the optic and those of the ocular muscles.

Infiltrating tumours of the pons (gliomata), as a rule, do not give rise to obstruction of the Aqueduct of Sylvius, hence there usually is no papillœdema. Headache is frequently absent, probably because there is no internal hydrocephalus. In our cases headache was an early and severe symptom; signs of pyramidal tract involvement are prominent features in glioma of the pons. They were practically absent in our first two cases. Involvement of the sensory division of the 5th nerve is more apt to be present in infiltrating tumours of the brain-stem owing to implication of the ascending spinal root. Nystagmus is also more frequent in intrapontine lesions. Pain in the neck is rare in glioma of the pons, but is pronounced in extrapontine tumours and occurs especially on movement of the head.

Vascular lesions of the pons and medulla are apt to give rise to more definite and clearly defined syndromes, involving either the distribution of the superior cerebellar artery, the posterior inferior cerebellar artery, the vertebral artery and the basilar artery with its branches.

We wish to express our indebtedness to Dr. Foster Kennedy for permission to publish the two cases from the Neurological Service of Bellevue Hospital.

REFERENCES.

Cushing, Harvey. "Intracranial Tumours," Springfield, 1932, p. 102.

Friedman, E. D, Brock, S., and Denker, P. "Syphilis of the Cerebello-pontine Angle," *Journ. of Syphilis*, 1933, **17**, 330-38.

Furlow, L. T. "Intracranial Chordoma," *Arch. Neur. and Psych.*, 1935, **34**, 839-948.

Muller, H. "Ueber das Vorkommen, von Resten der Chorda- dorsalis bei Menschen nach der Geburt und über ihr Verhaltnis zu den Gallertgeschwulsten am Clivus," *Zeitschr. f. rat. Med.*, 1858, **2**, 202.

Ribbert, H. "Ueber die Ecchondrosis physalifora spheno-occipitalis, nach Untersuchungen von Hermann Steiner," *Centralbl. f. allg. Path. u. path. Anat.*, 1894, **5**, 457.

Selinsky, Herman. "Intracranial Chordoma," *Arch. Neur. and Psych.*, 1932, **28**, 413-16.

Virchow, R. "Untersuchungen über die Entwickelung des Schadelgrundes," Berlin, 1857.

THE EFFECTS OF DIENCEPHALIC STIMULATION ON URINARY BLADDER TONUS.

BY JOHN BEATTIE AND ALAN S. KERR.[1]

(*Research Laboratories, Royal College of Surgeons of England.*)

INTRODUCTION.

THE physiological phenomena to be described were observed in the course of a series of experiments undertaken to establish the rôle of the hypothalamus in the control of the activity of the abdominal viscera. The effects on the intravesical pressure produced by electrical stimulation of the hypothalamus were correlated with the various nuclei and tracts from which effects were obtained.

EXPERIMENTAL METHODS.

Cats were used throughout the series. Anæsthesia was induced by chloralose injected intravenously in doses of 50 milligrammes per kilo body-weight after a preliminary ether narcosis. The animals were kept warm and left undisturbed for a period varying from thirty minutes to two hours before stimulation was attempted.

The urethra was exposed through a short suprapubic incision and a glass cannula inserted about one inch from the bladder neck and tied into position so that the upper end of the cannula projected into the bladder. The abdominal incision was then closed. As soon as the cannula filled with urine it was connected to a direct-recording water manometer previously filled with warm water. A T-piece was inserted into the rubber tube connecting the cannula to the manometer, so that the bladder could be emptied and a known quantity of fluid (usually 25 c.c.) introduced into the bladder at the beginning of the experiment. The cross-sectional area of the manometer was 0·44 sq. cm., hence a rise or fall of 10 cm. was equivalent to a change in bladder volume of 4·4 c.c. As the pressure changes often reached this figure, the experimental results recorded are changes in bladder pressure with accompanying but known small changes in bladder volume. No attempt was made to eliminate completely variations in bladder volume.

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[1] Ernest Hart Memorial Scholar, British Medical Association and Thelwall Thomas Fellow of the University of Liverpool.

The head of the cat was fixed in the Souttar stereotaxic instrument so that the stimulating electrode could be introduced parallel to the line joining the external bregmatic point to the mid-point of the optic commissure. In order to eliminate as far as possible variations in the points stimulated, cats weighing between 2·5 and 3 kg. were used exclusively. It was found convenient to remove a rectangular area of bone from the top of the skull extending from 0·5 cm. in front of bregma to a distance posterior to bregma of about 3 cm. and measuring in width about 1 cm. on each side of the middle line. Bleeding was checked by bone wax, muscle implants and hot saline. Two longitudinal incisions, a few millimetres on each side of the longitudinal sinus, enabled the anterior and posterior ends of the exposed sinus to be clipped with Cushing's silver wire clips. The sinus and falx cerebri were removed between the clips. No significant changes in bladder tonus were observed during these manipulations provided the anæsthetic was satisfactory.

Bipolar stimulation was used. The electrode consisted of two fine platinum wires sealed in glass capillary tubes, the tubes being fused together after the platinum wires were fixed. The greatest diameter of the electrode was 1·4 mm. and shortest diameter 0·7 mm. The points were 0·5 mm. apart and projected the same distance from the glass capillaries. The electrode was fixed in a holder which was attached to the electrode carrier of the stereotaxic instrument. Stimulation was effected by break shocks from an induction coil, so arranged that the current strength used was just less than the minimal amount necessary to cause contractions when applied direct to an exposed muscle. The break shocks were applied at a frequency of 60 per second.

During the routine exploration the electrode was inserted at successive points in the middle line 2·5 mm. apart and at corresponding points along planes 2·0 mm. from the middle line. Our results suggest that the area of brain stimulated by the electrode did not exceed a sphere of 2 mm. diameter, as effective stimuli were usually sharply localized and effects obtained from any one point were not reproduced from points 2 or 2·5 mm. distant.

When the experiment was completed, glass rods were introduced into the brain parallel to the plane of entry of the electrode, two anterior to the most anterior and two posterior to the most posterior stimulating points and at known and equal distances from the middle line. Two rods at right angles to the plane of entry were introduced at known distances from the middle line and in a plane at known depth from the bregmatic point. The brain was fixed with the rods in situ by injection through the aorta of 10 per cent. formalin after preliminary washing with normal Ringer or saline solution. The head was removed and immersed in 10 per cent. formalin for at least forty-eight hours.

Blocks were prepared after double impregnation with celloidin and paraffin. Sections were cut at 40 microns. In the early experiments sections were cut in the frontal plane and parallel to the plane of entry of the electrode, but in the later work a horizontal plane at right angles to the plane of entry was used. This had the advantage that all stimulated points could be seen on a single slide. The shrinkage factor was determined at 8-10 per cent.

Each alternate pair of sections was mounted so as to give two series of sections (*a*) a cell series, stained with cresyl violet, and (*b*) a fibre series, stained with Weil's iron hæmatoxylin (Weil, 1928). The tracks made by the electrodes were usually marked by areas of extravasated blood. In the fibre series a pale unstained zone surrounded the hæmorrhage at the tip of the electrode track. This zone did not measure more than 2 mm. in diameter. Such a zone was found only at the tip of the track and only when a stimulating current had been used. It may be taken, therefore, as some indication of the extent of the area stimulated.

The conventions used in indicating a specific point of stimulation indicate the distance from the bregmatic point in three planes. The zero line is the line joining the bregma to the mid-point of the optic commissure, the electrodes always being inserted parallel to this line. Point 0·25 thus indicates that the point stimulated is on the middle plane (antero-posterior) in the bregmatic line and 25 mm. below bregma, while Point 1·25 indicates a point in the middle plane 2·5 mm. posterior to bregma and at a depth of 25 mm. below the horizontal plane passing through bregma. Point 3·25·2 R. indicates a Point 7·5 mm. behind bregma in an antero-posterior plane, 25 mm. below the horizontal plane through bregma, and 2 mm. to the right of the middle plane. Thus the references to the antero-posterior plane are indicated by figures which give the distance from the bregmatic point in multiples of 2·5 mm.

EXPERIMENTAL RESULTS.

Stimulation of the Posterior Hypothalamus and Upper Mid-brain.

The most striking phenomenon which we observed on stimulation of this region was a complete inhibition of bladder tonus, with cessation of any spontaneous contractions of the organ. In Cat 29 (fig. 1) the electrode was introduced into the brain in the middle line 15 mm. behind the bregmatic point and 25 mm. below the level of bregma (Point 6·25). The mechanical stimulus caused by the introduction of the electrode produced relaxation of the bladder musculature. Electrical stimulation maintained this inhibition, but normal activity returned within one minute of the cessation of stimulation and withdrawal of the electrode.

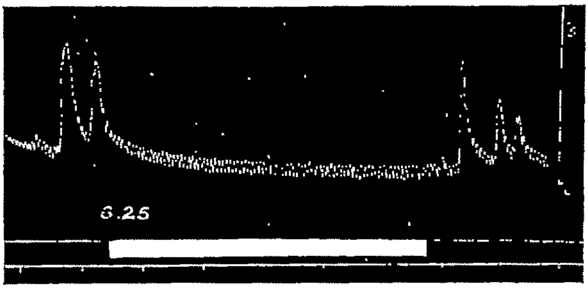

FIG. 1.—Fall in intravesical pressure and abolition of spontaneous rhythmic contractions on stimulation of the posterior and dorsal portion of the nucleus hypothalamicus posterior. Pressure in cm. of water and time marker in minutes.

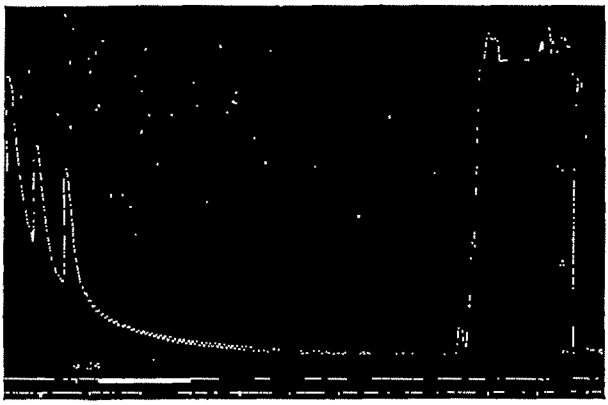

FIG. 2.—Fall in intravesical pressure and abolition of spontaneous contractions in a very "active" bladder. Note the complete absence of activity for 5½ minutes after cessation of the stimulus. The "rebound" phenomenon is well demonstrated. Pressure in cm. of water and time marker in minutes.

During the period of inhibition small waves are seen on the tracing which are synchronous with respiration and are due to transmitted pressure through the abdominal cavity.

In Cat 30 (fig. 2) the bladder was unusually active, showing large oscillations in pressure which were not synchronous with respiration.

When the electrode was introduced pressure fell rapidly, and on electrical stimulation remained low for a period of five and a half minutes after the cessation of the stimulation. Pressure returned to normal very rapidly. The point stimulated was in the middle line 15 mm. posterior to the bregma and 24 mm. below the level of this point (Point 6·24). The fall in bladder tonus on stimulation in the region of the upper mid-brain (Point 5·23) is particularly well marked in Cat 71 (fig. 4 A). It was suggested to us by Barrington that these inhibitory effects may be due entirely to the stimulation of the adreno-secretory nuclei or pathways in the hypothalamus with a consequent release of adrenalin. That adrenalin does give marked inhibition of bladder tonus can be seen in fig. 4 B (Cat 71). It was thus necessary to demonstrate whether the release of adrenalin into the circulation formed the whole or only part of this inhibitory mechanism. Stimulation at Point 6·28 in one animal (Cat 49) gave a typical inhibition of bladder tonus with rapid recovery to normal activity on cessation of stimulation (fig. 3 A). After complete ligation of the adrenal vessels the same point was stimulated with a resulting fall in bladder tonus (fig. 3 B). Further stimulation at this point some minutes later produced an identical effect. After the animal was killed a solution of Prussian blue was forced under pressure into the inferior vena cava in an attempt to drive some of the substance into the adrenal glands, but without success.

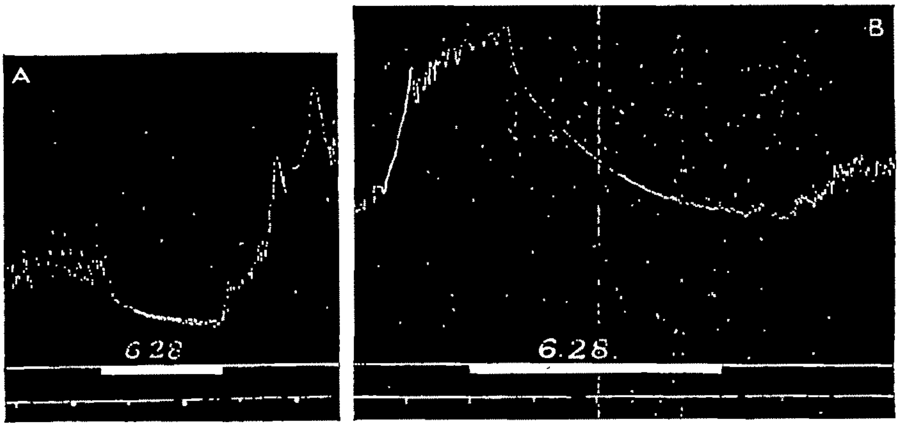

FIG. 3.—(A) Fall in intravesical pressure and abolition of spontaneous contractions on stimulation of Point 6·28, with "rebound" on cessation of stimulus. (B) After exclusion of adrenalin from the general circulation, stimulation of the same Point 6·28 is still effective.

In another animal complete inhibition of bladder tonus was obtained (fig. 4 A) by stimulation at Point 5·23. After one dose of ergotamin

(0·5 mgm.) 1 mgm. of adrenalin still produced well-marked inhibition of bladder tonus. Another 0·5 mgm. dose of ergotamin (seven minutes after the first) was administered and Point 5·23 stimulated five minutes after this injection. The effect produced was less well marked (fig. 4 B). Five minutes later 1 mgm. of adrenalin produced but little effect, and two minutes later stimulation at Point 5·23 gave a very slight fall in bladder pressure (fig. 4 C). After the second injection of ergotamin it was noted that the bladder pressure rose steadily reaching 15 cm. H_2O, beyond which it was not possible to record it. After stimulation at Point 5·23 for the third time, 10 mgm. of atropin injected intra-

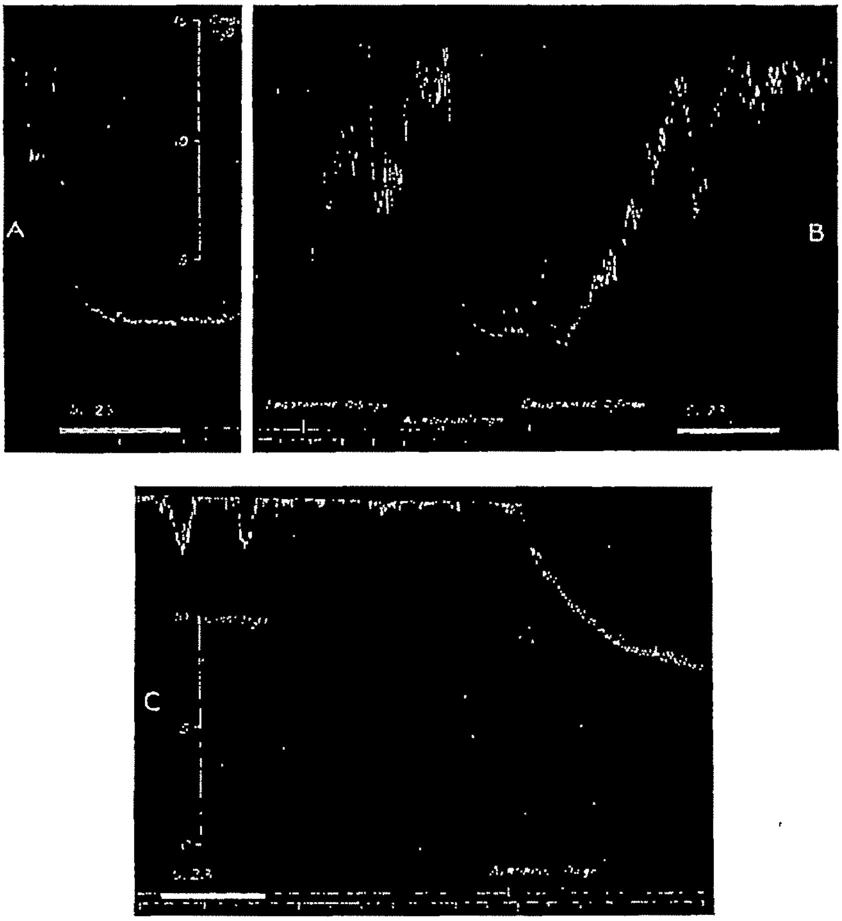

FIG. 4.—The effects on intravesical pressure of posterior hypothalamic stimulation (Point 5·23) and the modification of the response by ergotamin and atropin (see text). Time marker in minutes.

venously produced a steady decline in bladder pressure which eventually reached almost zero level (fig. 4 c). It would seem, therefore, that the region stimulated in these experiments contains not only adreno-secretory fibres and cells, but also fibres and cells which can influence the bladder directly, producing in that organ the typical sympathetic effect—relaxation.

Stimulation of the Anterior Region of the Hypothalamus.

The phenomena which we observed during stimulation in this area were essentially the reverse of those recorded for the posterior hypothalamus, that is, there was a rise in bladder pressure during stimulation with some increase in the height of the spontaneous bladder contractions in some experiments. Of these two effects the former was much more constant. The type of response obtained from stimulations in this region depended to a great extent on the state of activity of the bladder before stimulation was applied. When the bladder displayed little or no spontaneous contractions the result of stimulation was an increase in intravesical pressure, but when the bladder was active and showed great oscillations in pressure the tonic effect was masked to some extent by these oscillations. Fig. 5 A shows an animal with a moderately active bladder responding to a stimulus in the anterior hypothalamus (Point 0·25) by a marked rise in tonus with little or no effect on the spontaneous contractions. The same animal showed at a later stage of the experiment a very decided diminution in the contractions, but the tonic effect was equally well marked on stimulation of the same point.

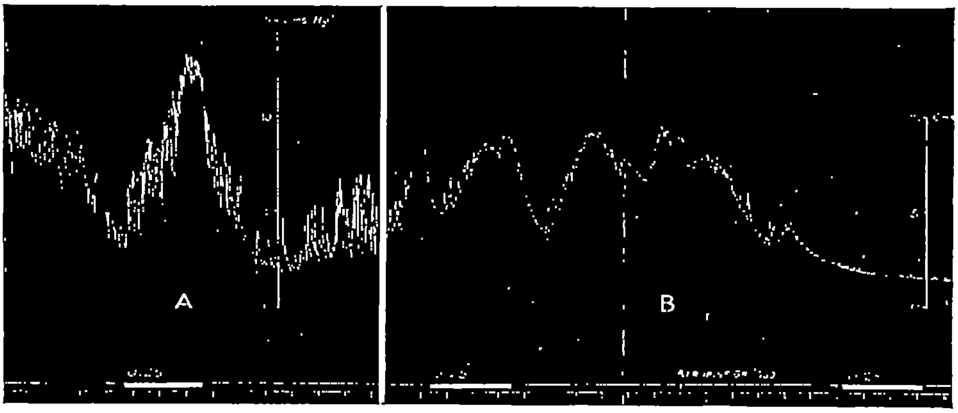

FIG. 5.—The effect of anterior hypothalamic stimulation (Point 0·25), showing increase in bladder tonus and abolition of the effect after atropinization. Time in minutes.

The activity of this bladder was remarkable, as there was a spontaneous rhythmic variation in the intravesical tension which occupied fully four minutes to complete a cycle. The pressure climbed by a series of well-marked contractions to a maximal point, and then declined relatively rapidly. During the decline the spontaneous contractions were absent. On stimulation of the anterior hypothalamus (Point 0·25) during the period of decline, the tonic effect was produced, but on cessation of the stimulus the pressure fell rapidly and the cycle of rise and fall in tension commenced again (fig. 5 B). The injection of atropin abolished not only the intravesical pressure but also the spontaneous contractions of the organ. Stimulation of the point (0·25) mentioned previously, did not produce the pressor effect, nor did the stimulation of a point (4·25) which had previously caused a fall in bladder tonus produce any further

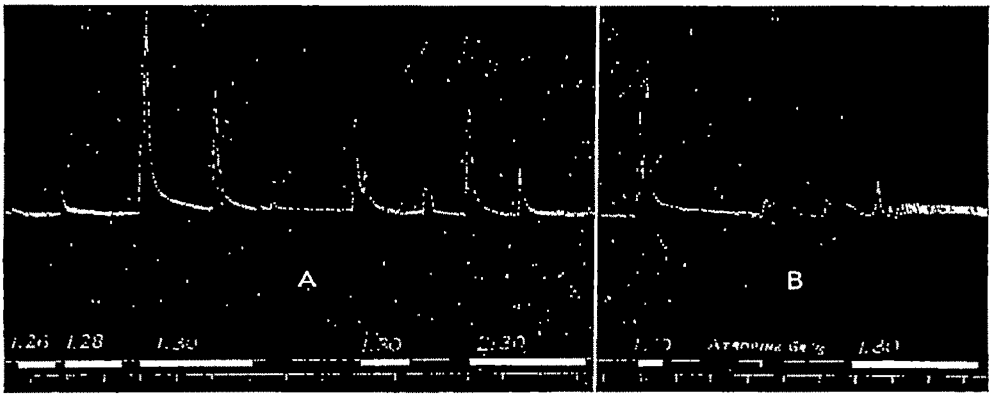

FIG. 6.—Rises in intravesical pressure from stimulation points in the tuber cinereum and upper mid-brain (Points 1·30 and 2·30). Abolition of the effect by atropin. Time marker in minutes.

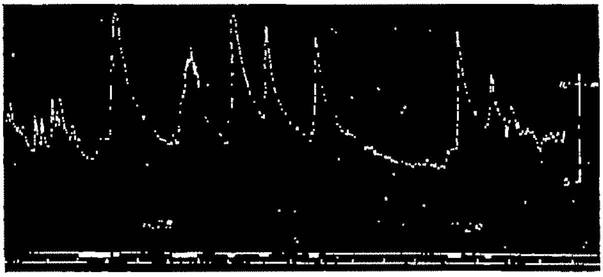

FIG. 7.—Rises in intravesical pressure on repeated stimulations at Points 6·28 and 7·28 (block signals) lying close together in the white matter on the dorsal surface of the grey matter of the aqueduct at the level of the inferior colliculi. Pressure in cm. water Time marker in minutes.

ABBREVIATIONS FOR PLATE FIGURES.

A. = Aqueduct of Sylvius.
C.I.C = Commissure of the inferior colliculus.
F. = Fornix.
I.C. = Inferior colliculus.
I.P.S. = Inter-peduncular space
I.R. = Infundibular recess.
M.B. = Mammillary body.
M.T.T. = Mammillo-thalamic tract (Vicq d'Azyr).
N.E.W. = Nucleus Edinger-Westphal.
N.R. = Nucleus rubra.
N.T.C. = Nuclei of posterior tuber cinereum.
P.C. = Posterior commissure.
T.P.T. = Thalamo-peduncular tract.
V. III = Third ventricle.

Points 0·25, 1·30, &c. = corresponding stimulating points in text-figures.

PLATE.

Fig. 1.—Section cut in frontal plane showing tip of electrode track at the periphery of the grey matter on the floor of the aqueduct. Stimulation of this point produced a fall in intravesical pressure. × 10.

Fig. 2.—Horizontal section through dorsal region of diencephalon to show stimulation point (5·23) of text-figure 4. × 10.

Fig. 3.—Horizontal section to show stimulation point (6·28) of text-figure 3. Point lies close to ventral surface of aqueduct grey matter. × 10.

Fig. 4.—Horizontal section to show stimulation point (0·25) of text-figure 5. Point lies in periventricular fibre system. × 10.

Fig. 5.—Horizontal section through tuber cinereum and mammillary bodies to show stimulation point (1·30) of text-figure 6. Point lies amongst the fibres of supra-mammillary decussation. × 10.

Fig. 6.—Horizontal section through dorsal region of mid-brain. Stimulation points (6·28 and 7·28) lie amongst the longitudinal fibres on the ventral surface of the decussation of the inferior colliculi (text-fig. 7) × 10.

PLATE III.

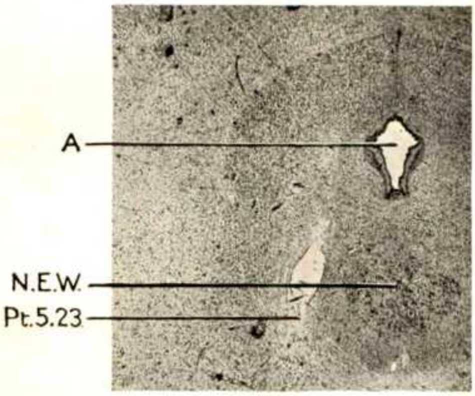

Fig. 1

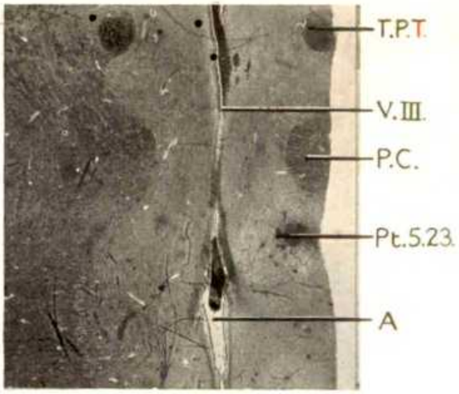

Fig. 2

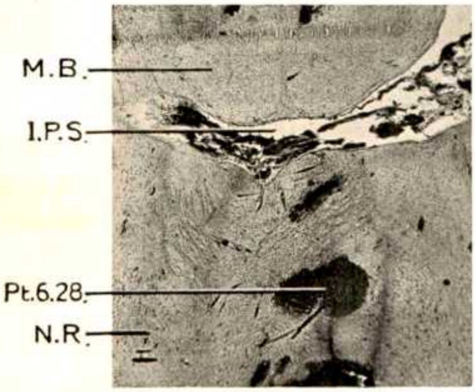

Fig. 3

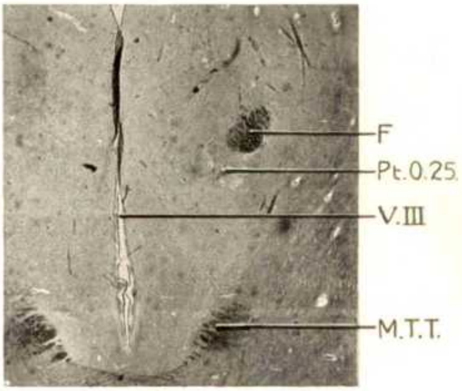

Fig. 4

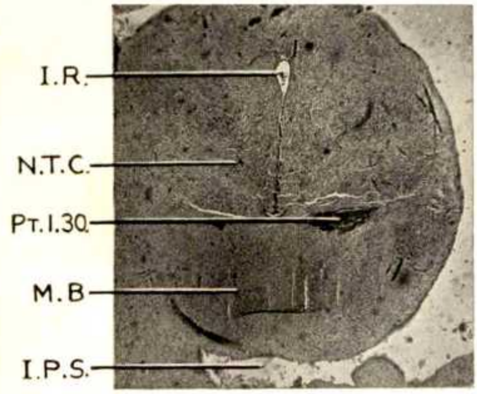

Fig. 5

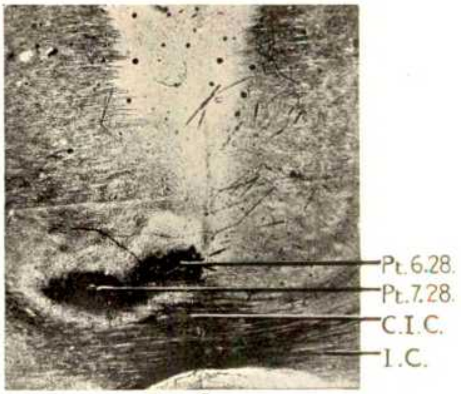

Fig. 6

To illustrate paper by John Beattie and Alan S. Kerr.

decline in bladder pressure when stimulated. The effective pressor area is apparently well circumscribed. Stimulation of adjacent points distant from it two millimetres or more gave no response, except along a well-defined tract running posteriorly.

Tracing 6 A from Cat 69 shows the effect of stimulation of the posterior part of the tuber cinereum (1·30) and of a point 2·5 mm posterior to 1·30 on a hitherto inactive bladder. There is a sharp rise in tonus which is not maintained throughout the period of stimulation. This effect was twice repeated, but after the injection of 12·5 mgm. of atropin, further stimulation was almost wholly ineffective (fig. 6 B). Cat 54 (fig. 7) shows the effect of stimulation of the dorsal part of the lower mid-brain. It again reveals very sharp rises of tonus maintained for a short time at micturition level, but falling rapidly as soon as stimulation ceases. We regarded these effects as being due probably to the stimulation of fibre pathways passing from the anterior hypothalamic region posteriorly into the brain-stem.

Histological Localization of Effective Stimulation Points.

In the previous section the effects of stimulation were discussed in terms of linear co-ordinates measured along three reference planes at right angles; it is necessary, therefore, to correlate these various effective stimulation points with various nuclei and tracts of the hypothalamus.

All the points which on stimulation gave rise to a diminution of intravesical pressure lay behind the level of the pituitary stalk, i.e. in the posterior part of the hypothalamus. More precisely these effective points were related to the nucleus hypothalamicus posterior or its backward continuation into the ventral part of the grey matter of the sylvian aqueduct. The most effective stimulation points were found to lie in the periphery of the grey matter of the floor of the aqueduct just caudal to its junction with the third ventricle. The reason for this is obvious when one remembers the widely scattered cells of the nucleus hypothalamicus posterior, and the concentration of the projection tracts from this nucleus into the peripheral region of the floor and lateral wall of the aqueduct.

The first two figures on Plate III indicate the anatomical relation of the efferent sympathetic tracts to the aqueduct. Plate III, fig. 3 is of interest, as the effective stimulation point is almost exactly in the middle line and has stimulated the fibre tracts which lie on the periphery of the grey matter of the aqueduct floor (see text-figs. 3 A and 3 B).

The experiments which have been described above leave no room for doubt that fibres related directly to the bladder in addition to adrenalo-secretory fibres are present in this region. In the same region, too, are the fibres which Beattie, Brow and Long (1930) showed to be related to the sympathetic control of the heart.

Increased intravesical pressure and increased rhythmic bladder contractions were obtained from a much more anterior region. Again, the most striking results on bladder tonus were obtained from regions where there is a considerable concentration of fibre tracts and not from the diffuse nuclear masses.

Plate III, fig. 4, demonstrates an effective stimulation point (text-fig. 5) just caudal to and slightly internal to the fornix bundle. Examination of the sections stained for fibres shows that this point lies in the periventricular fibre system. As the fibres of this system pass posteriorly some swing medially and cross the middle line in the supra-mammillary decussation. Stimulation of these decussating fibres also produces an increase in bladder pressure. (Plate III, fig. 5 and text-fig. 6 A and B.) The histological sections demonstrate that the fibre tracts are passing between the nuclei tuberis and the upper poles of the mammillary bodies. More posteriorly the fibre tracts have been shown to lie in the dorsal part of the periphery of the grey matter of the aqueduct (Plate III, fig. 6 and text-fig. 7). In the section shown the fibre tracts are stimulated as they lie anterior to the commissure of the inferior colliculus.

Our experiments do not indicate precisely which of the anterior hypothalamic nuclei can be regarded as the site of origin of these fibre tracts. One of the cell masses in the supra-optic or pre-optic areas may be concerned, but the presence in these regions of numerous fibres of passage does not allow us to regard effects obtained from them as "nuclear" rather than "tract" effects.

DISCUSSION.

Since the classical experiments of Elliot (1907) in which he established the double innervation of the urinary bladder, many workers have tried to distinguish the exact functions of the nerves. Regarding the fundus of the bladder, opinion as a whole is agreed that the pelvic nerves are motor to the detrusor muscle while the hypogastric nerves inhibit. The internal sphincter of the bladder has the hypogastric nerve as its motor supply, while the pelvic nerves are inhibitory. Henderson and Roepke (1934) have recorded an increase in intravesical pressure following the injection of acetylcholine. This effect is not produced if a previous injection of atropin is administered. This finding is in opposition to the view of Macdonald and M'Crea (1930) that drugs having either parasympathetic or sympathetic pharmacological actions may give rise equally to motor or inhibitor effects.

In this paper we are dealing only with the control of bladder tonus and not with the mechanism of micturition. In Barrington's (1921, 1925, 1927, 1933) work on the control of micturition he has recognized five centres for the control of this reflex act, two of which lie in the brain-stem. Only one of his experiments suggests a level of control above the upper pons in the cat. Langworthy and Kolb (1933) found that transection of the mid-brain at the level of the anterior part of the superior colliculi did in some way interfere with the intravesical pressure, for they found that in such animals the amount of water required to be introduced into the bladder, to raise its internal pressure to that level necessary to produce micturition, was much less than normal. This would suggest that, above the level of the transection, there is some mechanism for the inhibition of the smooth muscle of the bladder.

In our experiments the results suggest that there is not only a mechanism for the inhibition of bladder tonus, but also an additional one which can increase the bladder tonus much above the normal level. The histological findings lead us to believe that the former reaction is obtained from the posterior hypothalamic nuclei and their projection tracts which surround the floor and lateral wall of the grey matter of the aqueduct. In the case of the latter reaction the pressor effect is obtained from the more anterior hypothalamus, the nuclei concerned being probably in the supra-optic or pre-optic areas. Where the pressor effects were obtained from stimulation of the posterior hypothalamus and dorsal part of the aqueduct fibre system, it seems logical to suggest that these are due to stimulation of efferent pathways from more anterior nuclei passing through these regions.

CONCLUSIONS.

(1) The effects of controlled and histologically localized electrical stimulation of the hypothalamus and upper mid-brain on the tonus and activity of the urinary bladder are described.

(2) Evidence of the existence of centres for the increase of tonus in the anterior hypothalamus and for inhibition of tonus in the posterior hypothalamus and upper mid-brain is adduced.

(3) Bladder inhibition, due to hypothalamic stimulation, is produced

by the activation of direct nervous pathways to that organ, and also by the stimulation of adrenalo-secretory fibres.

(4) The striking responses obtained by stimulation of the mid-brain are explained as being due to activation of effector pathways in the white matter on the periphery of the central grey matter of the aqueduct of Sylvius.

We wish to express our thanks to Mr. S. P. Steward and the technical staff of the Royal College of Surgeons for their assistance at all stages of the work.

REFERENCES.

Barrington, F. J. F. *Brain*, 1921, **44**, 23.
Idem. Quart Journ. Exper. Physiol., 1925, **15**, 81.
Idem. Proc. Roy. Soc. Med., 1927, **20**, 722.
Idem. Brain, 1933, **56**, 126.
Beattie, J., Brow, G. R., and Long, C. N. H. *Proc Roy. Soc.*, Series B, 1930, **106**, 253.
Beattie, J., and Sheehan, D. *Journ Physiol.*, 1934, **81**, 218
Cloake, P C., Learmonth, J. R. and Barrington, F. J. F. *Proc. Roy. Soc. Med*, 1932, **25**, 547.
Elliott, T. R. *Journ. Physiol.*, 1907, **35**, 367.
Henderson, V. E., and Roepke, M. H. *Journ. Pharmaccl. and Exper. Therap*, 1934, **51**, 97.
Ingram, W. R., Hannett, F. I., and Ranson, S. W. *Journ Compt. Neurol*, 1932, **55**, 333
Kabat, H., Magoun, H. W., and Ranson, S. W. *Arch. Neurol. and Psych.*, 1935, **34**, 931.
Langworthy, O. R., and Kolb, E. *Brain*, 1933, **56**, 371.
Langworthy, O. R, Reeves, D. L., and Tauber, E. S. *Ibid*, 1934, **57**, 266.
Learmonth, J. R. *Ibid.*, 1931, **54**, 147.
Macdonald, A. D., and M'Crea, E. D'A. *Quart Journ. Exper. Physiol*, 1930, **20**, 379.
Rioch, D. McK. *Journ. Compar. Neurol.*, 1929, **49**, 1, 121.
Idem. Ibid, 1931, **53**, 319.
Weil, A. *Arch. Neurol. and Psych.*, 1928, **20**, 392.

FURTHER OBSERVATIONS UPON GRASPING MOVEMENTS AND REFLEX TONIC GRASPING.

BY F. M. R WALSHE AND J. H. HUNT.

Psychological and Reflex Factors in the Production of Grasping Phenomena.
The Influence of Apraxia and Hypertonus.
Relationship between Grasping Phenomena and the Righting Reflexes of Magnus and de Kleijn.
Summary.
References.

Psychological and Reflex Factors in the Production of Grasping Phenomena.

Observations recorded in this journal [7] by Walshe and Robertson led them to conclude that in the complex of phenomena known as "forced grasping" there are two distinct and separable components. These are (i) *volitional grasping movements* in response to objects seen, or to contacts felt in the palm of the hand, and (ii) *reflex tonic grasping* in response to stretching of the flexor muscles of the fingers.

The physiological significance of each of these components was discussed in the paper in question.

A further series of cases has since been investigated by the present writers with a view to studying separately the visual, tactile and proprioceptive factors in stimulation. For this purpose use was made of the method of blocking the cutaneous nerves to the hand, median, ulnar and radial, with novocain. The hand was thus rendered anæsthetic and the tactile factor eliminated. If, in addition, the patient was blindfolded, vision was also excluded and the factor of stretch could be observed in isolated operation.

The modifications introduced into the grasping phenomena by the presence of apraxia and of hypertonus in the affected limb have also been considered. In one case, also, it was possible to elicit from the patient useful information as to the mental factors which in him determined the occurrence of grasping.

Case 1.—F. A., a man aged 47. (National Hospital, 1935.)

History.—Subject for three months to Jacksonian attacks involving the right hand and leg. No loss of consciousness. For a month a slowly progressive right hemiparesis had been developing. It had become difficult for him to concentrate his attention, and he was said to have become a little "simple" in the past few weeks.

General examination.—Fully conscious and co-operative. Attention not normally sustained. Speech normal. Bilateral papillœdema (2D. right and left). Slight weakness of left external rectus with diplopia to left. Slight paresis of right lower face. Tongue protruded straight,

Slight right-sided hemiparesis with just appreciable hypertonus in the flexors of the upper and the extensors of the lower limb. The range of unresisted movement is full. In the hand there is slight weakness of grasp and a trace of clumsiness of finger movements. All forms of sensation are normal. The tendon jerks are brisker on the right than on the left, the right abdominal reflexes are diminished, but both plantar responses are of normal flexor type.

(i) *The patient's account of his grasping movements.*—During the various examinations of this man, his own comments upon the grasping propensities of his right hand were of considerable interest. He said: "I can't leave things alone. If I see anything lying near me, my hand seems to want it. At meal time my hand butts in and picks up things I don't want." "If I happen to look at something my hand seems to want it." "If I'm standing near a door I can't help catching hold of the handle, even if I know I don't want to open it, but just if the idea of opening it comes to me." "My hand—and not me—seems to want it."

(ii) *Examination of grasping movements.* — During one conversation a cigarette was laid upon the bed near his right hand, the patient sitting up in bed at the time. Every twenty or thirty seconds the right hand stole out towards the cigarette. Sometimes it was grasped, but at other times he suddenly seemed to notice what was happening and checked the right hand. Sometimes he seemed to find it easier to stretch out the normal left hand with which he grasped the right and pulled it back. This process was repeated many times. A wisp of cotton-wool was then substituted for the cigarette. After two grasping movements, the process stopped and in a few seconds the patient said, laughing, "My hand doesn't want it now." The cigarette was then replaced, and the process resumed with its original persistence. It appeared that the attractiveness of the object seen determined in a measure its potency as a stimulus to grasping movements.

His hand closes gently round the observer's fingers when these are introduced into his palm, and much more completely and rapidly when they are introduced between thumb and index than when they are introduced from the ulnar side.

He is able to relax a voluntary grasp (clenching) without difficulty, though not quite so rapidly as with the left (normal) hand, and this whether the hand be empty or whether it contains such an object as a fountain pen, or wooden rod. It may be noted that all movements of the right upper limb are slightly slower than those of the left, a fact which may be correlated with the slight paresis and hypertonus.

During the systematic testing of sensation on the palmar surface of hand and digits, no grasping movements were observed.

(iii) *Examination of reflex tonic grasping.*—No tonic grasping was observed unless the fingers were passively extended and stretch put upon the flexor muscles. In these circumstances typical tonic grasping ensued; but this could be relaxed by the patient on request, slowly and with apparent effort.

(iv) *Median nerve blocking.*—Two per cent. novocain solution was injected into the median nerve one inch proximal to the wrist line. Complete cutaneous anæsthesia and analgesia was obtained over the median nerve area.

Grasping movements.—When observer's fingers are introduced into the palm, the patient's eyes being blindfolded, no grasping movement is seen until the finger tips reach the area of normal sensation on the ulnar side of the palm. If they be introduced from the ulnar side there is some flexion of the fingers, most marked of the little and ring fingers. If the patient be allowed to look at his hand during this procedure, grasping movements ensue even when contact is confined to the anæsthetic area of the palm.

Reflex tonic grasp.—This is wholly unimpaired in intensity despite the insensitiveness of the skin of the hand. Using a spring balance with an attached loop which was passed round the flexed fingers singly, the following tensions were obtained before the finger was pulled out straight. Index. 20 lb.; middle finger, 15 lb.; ring finger 15 lb.; and little finger 14 lb.

(v) *Median, ulnar and radial nerve blocking.*—On a subsequent occasion both median and ulnar nerves were blocked above the wrist, and the radial nerve in the lower third of the forearm with 2 per cent. novocain solution. The hand became completely anæsthetic to touch, pin-prick, heat and cold to a line about one inch proximal to the wrist. *With the patient's eyes open* grasping movements occurred when the palmar aspect of hand or fingers was touched by the observer's fingers, and also when a cigarette was placed on his palm. With the patient's eyes covered no trace of grasping movement ensued when passive extension of the fingers was eliminated by placing the hand palm upwards upon a plaster cast made to the dorsum of the hand. In these circumstances, touch and pressure were without effect.

Reflex tonic grasp.—As in the previous observation, the response to stretch of the finger flexors remained wholly unimpaired in intensity, and it was clear that stretch was the sole operating stimulus.

All the familiar features of grasping movements and of reflex tonic grasping as recorded by Walshe and Robertson are exemplified in this case. The primacy of psychological factors in the causation of the grasping movements is particularly well illustrated. An object seen acts as a stimulus in respect of the ideas with which it has come to be associated in the patient's mind, and in respect of the emotional tone accompanying these ideas. A stimulus is adequate in respect of its place in the individual experience of the patient. Thus, a cigarette has become a more desirable object than a wisp of cotton-wool and for this reason, and this reason alone, acts as a more potent stimulus to grasping movement.

The decisive role of psychological factors in determining the adequacy of tactile stimuli to elicit grasping movements was apparent in the observations already referred to (7).

Fulton still maintains [3] that these volitional movements are as wholly reflex as the invariable tonic grasping which persists even in the unconscious patient. He does this in virtue of a belief that "the one fundamental tenet in the creed of modern neurophysiology" is the reflex nature of all possible movements. Tenets and creeds belong to other disciplines than that of science, and in fact this objection was fully discussed by Walshe and Robertson. Arguing upon the same lines as these writers, Creed [2] has recently put the position quite clearly; thus: "To many it would seem advisable to confine the use of so well-established a technical term as 'reflex' to the concept for which Marshall Hall in 1833 introduced it into the vocabulary of science, namely, to describe responses dependent upon inherited structure in the nervous system and not on individual experience. Hall considered that 'the excited motions which belong to the reflex function are independent of sensation.' Unless it can be proved that consciousness is an ineffective bye-product of central nervous activity, it is probably wise for us to exclude from the category of reflex action all phenomena in which mental activities may play an essential part." We may therefore continue, without fear of physiological heresy, to regard the movements in question as volitional, though probably of the kind that Jackson would have called "least voluntary, most automatic."

This case also exemplifies the fact that reflex tonic grasping has as its sole adequate stimulus stretch of the flexor muscles of the fingers, and persists unimpaired when both visual and tactile stimuli have been eliminated. It is a proprioceptive reaction, completely independent of volition or of any mental activity.

The use of nerve blocking of the cutaneous supply of the hand was adopted in a second similar case, and with results identical with those described above.

THE INFLUENCE OF APRAXIA AND OF HYPERTONUS.

It was emphasized by Walshe and Robertson that the subject of "forced grasping" could open his clenched fist easily when it was empty and even when it contained an object which was not being pulled away so as to stretch the flexors of the fingers. Occasionally a case may be seen in which the subject appears to have more or less difficulty in relaxing the grasp of his empty hand. This apparent exception to the general rule does not necessitate any revision of our view as to the cause of tonic grasping, and it is, in our experience, always due to the intervention of other factors. Apraxia is perhaps the most important of these, and the patient's inability to open his empty fist on request in a case of reflex tonic grasping is commonly due to apraxia. The following case illustrates this.

Case 2.—*Glioma in right parietal lobe. Voluntary grasping movements, reflex tonic grasping and apraxia of left hand.*

H. A., a man aged 48. (National Hospital, 1935.)

History.—Two months history of Jacksonian attacks of the left arm, with progressive hemiparesis of the left side.

General examination.—Fully conscious, but fatuous. Attention ill-sustained. No papillœdema. Slight left hemiparesis with just appreciable hypertonus of the limbs, tendon jerks increased in left limbs, abdominal reflexes present on both sides, both plantar responses flexor. Left hemi-hypæsthesia to touch, pinprick, heat and cold, postural sense.

A right subtemporal decompression revealed a glioma (astrocytoma) in the right parietal region.

Tests for Apraxia.

Face.—Could carry out the following movements in order correctly and without error or delay: Put out tongue; Shut eyes; Show teeth; Shake head; Nod; Whistle.

	R.	*L.*
Arms.—Beckon.	Correct.	Says, "It won't come up," then extends index finger and says, "It won't move."
Shake fist.	Correct.	Clenches fist, then opens hand and looks at it. Says, "It won't come up."
Shake hands.	Correct.	Lifts hand to shake.
Open hand.	Correct.	No movement—then after a long pause opens it easily.
Touch thumb and little finger.	Correct.	Extends and abducts all digits and looks at them.
Finger to nose.	Correct.	Clenches fist, then opens it. Says, "It won't come up."
Brush hair with brush.	Correct.	Holds brush, does nothing. Says, "I can't get the brush up, it beats me."

	R.	*L.*
Strike a match on box.	Correct.	Opens box with right hand, takes out match with left and holds it against the side of the box without striking it. When it is struck for him, he blows it out spontaneously.
Put on glasses.	Correct.	Holds glasses and fumbles. Does not put them on nose.
Comb moustache.	Correct.	Holds comb and looks at it helplessly.
Clench fist.	Correct.	Makes a grasp, but cannot be induced to squeeze the dynamometer.

He was requested to make this last movement with the left hand a number of times on different occasions. The result was variable. At times a normally rapid opening was seen. At others he looked at the hand and was unable to relax the grasp, doing so easily a few seconds later when his attention was diverted to something else. This uncertainty of response obtained whether the closed hand was empty or contained an object, such as a roll of bandage or a pencil.

Grasping movements of the left hand showed the usual features. Thus, in systematic sensory testing of the hand no grasping movements occurred. There were grasping movements when the observer's hand was approached close to the patient's in the attitude of inviting to a handshake. Stroking of the patient's palm with the observer's fingers introduced between thumb and index also elicited rapid grasping movements.

Reflex tonic grasping in response to stretch was also present. The presence of apraxia had no influence upon this.

In two other similar cases in which apraxia co-existed with grasping movements and reflex tonic grasping in the same hand, this same uncertainty of response in opening, at request, the closed hand was also seen.

Perhaps less striking is the influence of hypertonus of the grasping limb. In the spastic arm of any case of residual hemiplegia voluntary movements are notably slow, and when voluntary extension of the fingers is possible it is a slow and laboured accomplishment. Similarly, if any degree of spasticity invades the limb which shows grasping movements, there is an increased delay in the voluntary relaxation of the clenched and empty fist, but this is a function of spasticity and impaired power of movement and not of the grasping movement itself.

Occasionally, indeed, in a very spastic residual hemiplegia in which there is no trace of grasping *movements* of the kind under consideration, namely the so-called "forced grasping," the permanent hypertonus of the flexors of the fingers may be felt to be appreciably increased by sudden passive extension of the fingers. This was well seen in the following case of old infantile hemiplegia.

Case 3.—*Infantile left hemiplegia. No grasping movements, but increased flexion of fingers in response to stretch.*

G. H., aged 17. (National Hospital, 1935.)

History.—Difficult labour. Began to walk when in third year. Fell unconscious (? epileptiform fit) when aged 10 years. Since this the left limbs have become very stiff and useless.

General examination.—Intelligent. Severe spastic left hemiplegia. The left arm is adducted, slightly flexed at the elbow, semipronated, all digits flexed except the thumb. Movements of the limb as a whole are slow, coarsely tremulous and limited in range. Voluntary grasp retains fair power.

The left leg is rigidly extended, with the foot inverted and plantar flexed. No voluntary dorsiflexion of foot.

Left tendon jerks very brisk, right normal. Left plantar response equivocal, right flexor.

Left hand and arm.—On request the flexed finger can be slowly extended, the movement taking three seconds to complete.

When the observer's hand is insinuated in the palm, there is no trace of closure round it, and no active grasping movement can be evoked by any kind of visual or tactile stimulus.

If the observer's index finger be curled under the semiflexed digits, and these are gently lifted (i.e. extended) a moderate degree of hypertonus can be felt, but if this extension be brusquely increased and sustained, then the hypertonus of the flexor muscles can be felt to increase notably and the flexed fingers retain the observer's finger—or a wooden rod—against considerable extending force.

This increased flexor tonus is undoubtedly a response to stretch, and as such is presumably allied to the reflex tonic grasping we have been considering. But the latter may be fully developed and powerful in the absence of any resting hypertonus in the affected muscles and cannot therefore be regarded simply as an expression of hypertonus.

Relationship between the Grasping Phenomena (Movements and Tonic Grasp) and the Righting Reflexes of Magnus and de Kleijn.

Fulton [3] and Bieber and Fulton [1] report that after bilateral excision of Areas 4 and 6 in the monkey, the forced grasping shown by the animal varies with the animal's position in space. With the animal supine the extremities become extended and forced grasping becomes minimal or disappears. In the left lateral position only the right extremities exhibit grasping, and this can be inhibited by exerting pressure from above (Magnus's " Brettversuch.")

In their case of "syndrome of the premotor cortex in man" [4] which has been discussed by one of the present writers elsewhere [6] Kennard, Viets and Fulton report that in the human subject also the strength of the grasping phenomena varies with variations of the patient's position in space exactly as described above for the monkey.

From this they conclude that "the grasp is part of the righting reflex mechanism peculiar to primates" [3].

But even if these observations be confirmed, the conclusion drawn from them by Fulton does not follow, and it would be more accurate to say that grasping and the righting reflexes interact. Such interaction between reflexes of different physiological category is known to occur, and the influence of the tonic neck reflex upon the Babinski response as recorded by Walshe [5] is a case in point. We do not say, however, that the Babinski response is therefore part of the tonic reflex mechanism. Indeed, we know it is not.

Therefore indications of interaction between grasping and righting reflexes leave the existence of a relationship between them, and the possible nature of such a relationship, entirely open questions, and do not provide evidence of their identity. Indeed, so widely separate in their nature are grasping movements and reflex tonic grasping that it is difficult to see how both can be part of the same mechanism.

As to the fact of this interaction in man, no trace of influence of body posture in relation to space, or of head posture in relation to the trunk, upon either grasping movements or upon reflex tonic grasping could be found in any of our cases. We have thus been unable to confirm Fulton's observations.

SUMMARY.

Evidence is adduced to show that of the two components of "forced grasping" described by Walshe and Robertson: namely, voluntary grasping movements, and reflex tonic grasping, the former is determined by mental factors and cannot properly be called reflex, while the latter is exclusively a proprioceptive reflex reaction to stretch.

No evidence was obtained of any interaction between either of these components and the righting reflex mechanism of Magnus and de Kleijn.

Our thanks are due to those members of the Honorary Staff of

the National Hospital who have allowed us to examine and record their cases.

REFERENCES.

[1] Bieber, I., and Fulton, J. F. *Amer. Journ Physiol.*, 1935, **105**, 7

[2] Creed, R. S. *Nature*, 1934, **134**, 792.

[3] Fulton, J. F. *Arch. Neurol. and Psychiatr.*, 1934, **31**, 221.

[4] Kennard, M. A., Viets, H. R , and Fulton, J. F. *Brain*, 1932, **57**, 69.

[5] Walshe, F. M. R *Ibid.*, 1923, **46**, 281.

[6] *Idem.* *Ibid.*, 1935, **58**, 49.

[7] Walshe, F. M. R., and Robertson, E. G. *Ibid.*, 1933, **56**, 40.

THE EFFECT OF PROLONGED OCCLUSION OF THE EXTERNAL JUGULAR VEINS ON THE CEREBROSPINAL FLUID AND THE TORCULAR VENOUS PRESSURES OF THE DOG.

BY T H. B. BEDFORD.

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In an earlier paper [3] an account has been given of a number of experiments which were undertaken in order to study the effect of occlusion of the external jugular veins on the pressure of the cerebrospinal fluid and on the venous pressure in the torcular. It was found as a result of these experiments that the rise in the pressure of the cerebrospinal fluid which follows sudden occlusion of the external jugular veins is a temporary phenomenon, and that the pressure usually returns to the region of its original level within the space of one hour. The venous pressure in the torcular was also observed to fall, but the fall was not so rapid or so complete as the fall in the pressure of the cerebrospinal fluid, and at the end of the experiment the torcular venous pressure was sometimes more than twice its original height. These pressure changes were found to occur independently of variation in the systemic arterial pressure. The average duration of the experiments was two hours.

It was concluded that the fall in the pressure of the cerebrospinal fluid was due mainly to the formation of collateral venous circulation; it was also considered that there had probably been a reduction in the total volume of the cerebrospinal fluid. The experiments were conducted on fully anæsthetized and consequently immobile animals. The anæsthetic employed in these experiments was ether. The question naturally arises as to whether similar pressure levels would be found in active unanæsthetized animals, The following experiments were undertaken in an attempt to obtain information on this problem.

Before proceeding to a description of the experiments, it is necessary first to describe the precise point at which the external jugular veins were occluded. It was the custom to shave the necks of the animals in order to render visible the superficial veins. The vessels were occluded by ligation with catgut. The ligature was placed immediately below the level at which the external jugular vein receives its last tributary from the head. This point is usually situated on a level with the body of the fourth cervical vertebra. It is important to bear in mind that an occlusion of the vein at this point obstructs not only the blood which leaves the cranium through the post-glenoid foramen, but also a considerable amount of the blood from the muscles and soft parts of the head. Owing, however, to the great variations in the mode of termination of the tributaries of the external jugular veins which were encountered in different animals, it was felt that a more uniform degree of venous congestion could perhaps be obtained by ligating at this site than by attempting to occlude the vein at a higher level in the neck. For details of the intracranial venous system of the dog, reference should be made to previous publications [2, 3].

At an early stage in the investigation the external jugular veins were occluded in five dogs. The animals were allowed to survive for varying periods up to six weeks when they were killed. During post-operative life the animals appeared normal in all respects. A careful examination of the brains after death failed to reveal any evidence of hydrocephalus or of other abnormalities. It was also noted that the intracranial venous sinuses were free from clot and that the external jugular veins were patent close up to the ligatures. The internal jugular veins were found to be considerably dilated. It was evident from these experiments that occlusion of the external jugular veins does not cause hydrocephalus in dogs when the animals are observed for periods up to six weeks.

An attempt was now made to record the cerebrospinal fluid pressure and the torcular venous pressure in animals in which the external jugular veins had been occluded twenty-four hours previously. The experiments were conducted as follows: The dogs were anæsthetized with ether and the external jugular veins ligated at the site already indicated. They were then allowed to recover

TABLE I.

Dog No.	Cerebrospinal fluid	Torcular venous	Femoral artery
1	240	190	130
2	240	220	125
3	270	260	125
4	210	265	130
5	205	225	125

The cerebrospinal fluid pressure, the torcular venous pressure and the arterial pressure in the femoral artery in five dogs in which the external jugular veins had been occluded twenty-four hours previously. The pressure of the cerebrospinal fluid and the torcular venous pressure are recorded in millimetres of normal saline solution, the pressure in the femoral artery in millimetres of mercury.

from the anæsthetic and twenty-four hours later they were again anæsthetized and a simultaneous reading taken of the following pressures: (*a*) the cerebrospinal fluid pressure in the cisterna magna; (*b*) the venous pressure in the torcular; (*c*) the systemic blood-pressure in the femoral artery. The results of five experiments are contained in Table I. It will be observed that these readings show a close similarity to those obtained immediately after the external jugular veins had been occluded (Table II). These latter figures are extracted from an earlier publication [3].

TABLE II.

Dog No.	Cerebrospinal fluid	Torcular venous	Femoral artery
1	210	195	110
2	230	210	115
3	255	270	90
4	230	280	130
5	200	195	120

The cerebrospinal fluid pressure, the torcular venous pressure and the arterial pressure in the femoral artery in five dogs immediately after occlusion of the external jugular veins. The pressure of the cerebrospinal fluid and the torcular venous pressure are recorded in millimetres of normal saline solution, that in the femoral artery in millimetres of mercury.

The intracranial pressures were now recorded in animals in which the external jugular veins had been occluded for periods longer than twenty-four hours. High pressures were observed up to the third or fourth day, but after a week the cerebrospinal fluid pressure was generally normal while the venous pressure, although considerably reduced, was usually above its normal level. The pressure readings in four animals in which the external jugular veins had been occluded seven days previously are indicated in Table III. These findings were most unexpected. Experiments of two to three hours' duration on

TABLE III.

Dog No.	Cerebrospinal fluid	Torcular venous	Femoral artery
1	135	155	115
2	120	160	120
3	150	200	125
4	195	180	120

The cerebrospinal fluid pressure, the torcular venous pressure and the arterial pressure in the femoral artery in four dogs seven days after occlusion of the external jugular veins. The pressure of the cerebrospinal fluid and the torcular venous pressure are recorded in millimetres of normal saline solution, that in the femoral artery in millimetres of mercury.

animals which were not allowed to survive the anæsthetic had led one to anticipate a normal cerebrospinal fluid pressure, and a venous pressure which was very nearly normal in those which had been allowed to survive twenty-four hours. An attempt was now made to discover some cause for the raised pressures in these animals.

A careful examination was first made of the brain and its coverings in animals in which the external jugular veins had been occluded twenty-four hours previously. The brain and its coverings presented no abnormality either on naked-eye or on microscopic examination, if the precaution were taken to prevent a rapid escape of cerebrospinal fluid before death. There was no evidence of gross dilatation of the superficial vessels of the brain. The intracranial sinuses were free from clot and the external jugular veins were patent close up to the ligatures. The cerebrospinal fluid was normal. On the other hand, the brain usually presented definite abnormalities if the pressure of the cerebrospinal fluid was suddenly reduced before death by allowing quantities of the fluid to escape through the needle in the cisterna magna. The superficial vessels were markedly dilated and a careful scrutiny of the surface with a hand-lens generally revealed minute subpial hæmorrhages. Occasionally these hæmorrhages were abundant, but even then they usually remained discrete and there was never any evidence of gross bleeding. Usually however they were scattered, difficult to find and confined to the base of the brain. When the brains were examined histologically, the hæmorrhages were found to be restricted mainly to the grey matter of the cortex and the basal ganglia. In these cases, the cerebrospinal fluid, although normal to naked-eye inspection, usually gave a slight deposit of blood on centrifuging. There was also a slight increase in the total protein, but this was no more than could be accounted for by the presence of the blood. It is evident that these abnormal findings were directly dependent on the rapid decompression which had preceded death. Somewhat similar observations have been made by Ossipow [7] who found that hyperæmia and hæmorrhages in the brain followed lumbar puncture in dogs.

An attempt was now made to determine whether the return of the intracranial pressures to the region of their original levels within an hour of occluding the external jugular veins was caused by some error in the experimental technique. It was thought at one time that the fall in the pressure of the cerebrospinal fluid could possibly be accounted for by a leakage of cerebrospinal fluid along the side of the recording needle. To minimize the risk of leakage it was the custom always to reject results obtained from animals in which the dura had been punctured more than once. Nevertheless it was still possible that a gradual leakage of cerebrospinal fluid had occurred along the side of the recording needle. In order to determine whether the fall in pressure could be accounted for on such a basis the following experiments were performed. The external jugular veins were occluded in three dogs. Readings were taken of the venous pressure in the torcular and of the systemic blood-pressure in the femoral artery. At the end of an hour when the venous pressure was noticed to have fallen considerably, the cisterna magna was punctured with a needle and a reading taken of the cerebrospinal fluid pressure. In all three animals the cerebrospinal fluid pressure was found to be within normal limits. The blood-pressure remained steady throughout the experiments.

In the light of these experiments it is inconceivable that the fall in the pressure of the cerebrospinal fluid can be accounted for by a leakage of fluid along the side of the recording needle. The accidental introduction of hypertonic anticoagulant solution into the circulation during the washing out of the cannula employed to record the femoral arterial pressure was also thought to be a possible cause of the fall in the intracranial pressures in the acute experiments. Stringent precautions, however, were taken to avoid the possibility of any of the anticoagulant solution entering the circulation. The anticoagulant employed was an isotonic solution of sodium citrate. It is, therefore, highly improbable that the fall in the pressures could have been brought about in this manner. There does not appear to be any evidence for the belief that the phenomenon is the result of some error in the experimental technique.

It is generally admitted that the rapid rise in the pressure of the cerebrospinal fluid which occurs on occluding the external jugular veins is caused by a reflection of the rise of intracranial venous pressure in that of the cerebrospinal fluid. It would seem important to determine whether the raised cerebrospinal fluid pressure in the animals which had survived twenty-four hours was merely an expression of the raised intracranial venous pressure or whether an increase in the pressure of the cerebrospinal fluid—caused presumably by an increased formation of cerebrospinal fluid—had brought about a state of raised intracranial venous pressure. It is, of course, well known that changes in the pressure of the cerebrospinal fluid are unaccompanied by any change in the venous pressure in the torcular in animals in which the external jugular veins have not been occluded. On the other hand pressure changes in the intracranial venous system are always reflected in that of the cerebrospinal fluid [1, 3, 8, 9].

Unfortunately no information is available as to whether the pressures react in a similar manner in animals in which the external jugular veins have been occluded. The close similarity between the raised intracranial pressures observed immediately after occlusion of the external jugular veins and the pressures found after a survival period of twenty-

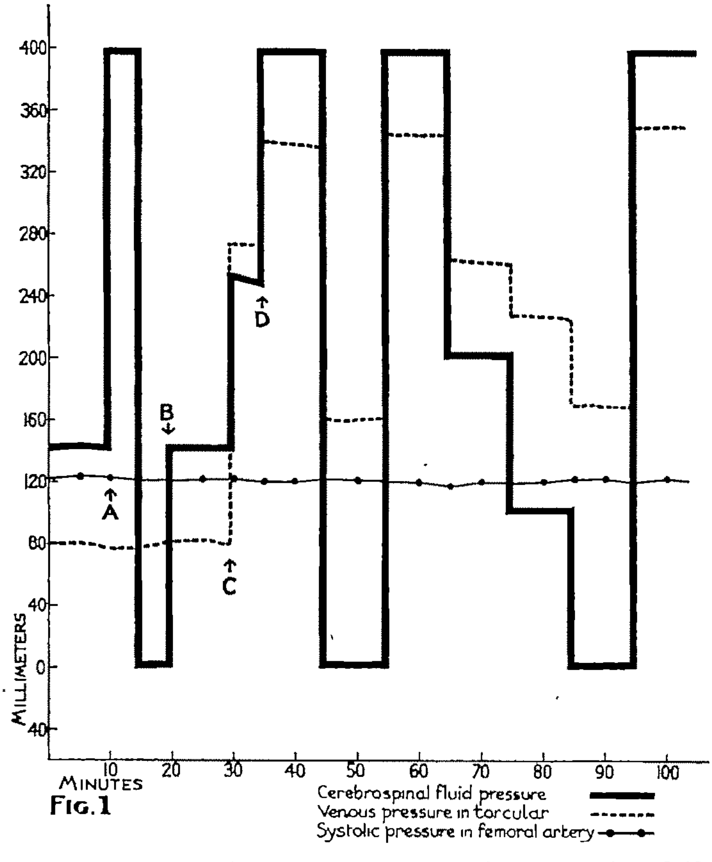

FIG. 1

FIG. 1.—The effect of variations in the pressure of the cerebrospinal fluid upon the venous pressure in the torcular before and after occlusion of the external jugular veins. A reservoir was attached to the manometer recording the pressure of the cerebrospinal fluid at A and the pressure varied. It will be observed that changes in the pressure of the cerebrospinal fluid are without influence on the venous pressure in the torcular. The cerebrospinal fluid pressure was set at its original level at B and at C the reservoir was detached from the manometer and the external jugular veins occluded. After the intracranial pressures had assumed new levels, the reservoir was attached to the manometer at D and the pressure of the cerebrospinal fluid varied. Changes in the pressure of the cerebrospinal fluid are now followed by changes in the same direction but to a lesser extent in the venous pressure in the torcular. The pressure of the cerebrospinal fluid and the torcular venous pressure are recorded in millimetres of normal saline solution, that in the femoral artery in millimetres of mercury.

four hours suggests very strongly that their origin is the same. Experiments were now undertaken to determine the effect of changes in the pressure of the cerebrospinal fluid on the venous pressure in the torcular in animals in which the external jugular veins had been ligated. Changes in the pressure of the cerebrospinal fluid are easily effected by attaching a reservoir containing saline solution to the base of the manometer recording the cerebrospinal fluid pressure. By raising or lowering the reservoir it is possible to set the pressure of the cerebrospinal fluid at any desired level.

Observations were first made on animals shortly after occlusion of the veins and while the intracranial pressures were still high. The investigation was restricted to a study of the effect of changes in positive pressure over a range of 0 to 400 mm. of normal saline solution. A fairly typical experiment is illustrated in fig. 1. The results of the experiments may be briefly summarized. Raising or lowering of the cerebrospinal fluid pressure was accompanied by changes in the same direction in the venous pressure in the torcular. The extent of the change in pressure in the torcular was found to average about 40 per cent. of the change in the cerebrospinal fluid pressure. This was the same both on raising and on lowering the pressures. Occasionally the change in the venous pressure was relatively slight. The smallest change observed in these experiments was 12 per cent. of the change in the pressure of the cerebrospinal fluid; on the other hand it was occasionally as great as 60 per cent.

Observations were also made on animals one hour after the external jugular veins had been occluded and when the cerebrospinal fluid pressure had fallen to the region of its original level. No evidence was obtained which might suggest that the amplitude of the change in the venous pressure was determined by the initial height of the pressures at the start of the experiment. The change in the venous pressure was usually complete after five seconds, and the pressure generally remained stationary after it had attained a new level. In these experiments the pressure of the cerebrospinal fluid was changed at intervals of five or ten minutes.

The experiments were repeated on animals in which the external jugular veins had been occluded twenty-four hours previously. It was found that the torcular venous pressure responded to changes in the pressure of the cerebrospinal fluid in a manner almost identical with that observed in animals immediately after occlusion of the external jugular veins.

Although the above description is that of the most frequent reaction of the venous pressure in the torcular to changes in the pressure of the cerebrospinal fluid after occlusion of the external jugular veins, variations were observed. The following was the most frequent and occurred to some extent in about a quarter of the experiments. A change in the pressure of the cerebrospinal fluid was accompanied by a variation in the same direction in the venous pressure which generally averaged about 40 per cent. of the change in the pressure of the cerebrospinal fluid. When, however, the pressure of the cerebrospinal fluid was restored to its original level, the venous pressure usually returned to a level somewhat higher than its original one. Subsequent manipulations of the cerebrospinal fluid pressure had less and less influence on the venous pressure and a longer period was required for this pressure to attain its new level. Finally, in some experiments the venous pressure remained entirely uninfluenced by changes in that of the cerebrospinal fluid. It was possible to show that clotting of blood in the torcular was not responsible for these results. It would seem highly probable that findings of this type were largely determined by the onset of œdema of the brain and possibly by volume changes in the intracranial vascular system subsequent to sudden lowering of the pressure of the cerebrospinal fluid.

Eyster [4] in 1906 observed during the course of a series of experiments in which it was necessary to maintain the intracranial pressure at a high level for a long period of time, that the brain sometimes became markedly œdematous. He seems to have held the view that the œdema was caused directly by the high intracranial pressure. He states, however, that when the œdema is once established "more or less blocking (of the subarachnoid space) may occur at the isthmus tentorii cerebelli, or at the cranio-vertebral junction."

Masserman and Schaller [5] in 1933 showed that rapid decompression of the ventriculo-subarachnoid space of the dog is followed by œdema of the brain. They believe that this may lead to a "partial œdematous closure of the aqueductus cerebri or subarachnoid block at the foramen magnum." In a more recent paper, Massermann [6] has brought forward evidence that the rapid removal of cerebrospinal fluid in man causes a vascular dilatation in the central nervous system which does not completely regress even if the fluid is immediately reinjected.

We are now in a position to consider whether the results of these experiments justify the conclusion that the raised cerebrospinal fluid pressure found after a survival period of twenty-four hours is directly dependent on the raised intracranial venous pressure, or whether an increase in the volume of the cerebrospinal fluid has brought about an increase in its own pressure and in the venous pressure in the torcular. Although the experiments provide no evidence against the first of these possibilities, they do, however, show quite clearly that an increase in the pressure of the cerebrospinal fluid in animals in which the external jugular veins have been ligated is accompanied by an increase in the venous pressure in the torcular. It would seem possible, therefore, to account for the pressure findings in the animals which had survived twenty-four hours on a basis of either possibility. The experiments fail to provide us with a means of deciding which explanation is the correct one. It should, of course, be borne in mind that the raised pressures may be due to a combination of causes.

Attention has already been drawn to the fact that the non-recovery experiments were conducted on animals which were fully anæsthetized and in which the anæsthetic was administered at a rate as near constant as possible. A very different state of affairs obtained in the recovery experiments. For a considerable part of the twenty-four hours the animals were active and alert, frequently changing the position of the head in relation to the rest of the body and at times barking or eating their food. It would not be surprising, therefore, if the embarrassed intracranial venous circulation, though able to maintain a fairly normal pressure in the immobile and fully anæsthetized animal, would be unable to do so in the active unanæsthetized animal. It should also be borne in mind that the external jugular veins receive blood not only from the interior of the cranium, but also from the greater part of the muscles and glands of the head. It is well known that during functional activity the blood-flow through these structures is enormously increased. This would add considerably to the embarrassment of the intracranial venous circulation in animals in which the jugular veins have been ligated. It is probable, however, that the most intense degree of venous congestion of the head occurs in these animals as a consequence of the marked embarrassment of respiration during the induction of the ether anæsthesia.

The effect of carbon dioxide on the diameter of the pial arteries of the cat has been carefully studied by Wolff and Lennox [10]. These observers measured the diameter of the pial arteries through a window in the cranium. They found that an increase in the carbon dioxide content of the blood brought about a considerable increase in the size of these vessels. This was usually accompanied by a marked increase in the pressure of the cerebrospinal fluid. The influence of carbon dioxide on the pial vessels was shown to be independent of changes in the systemic blood-pressure. A marked degree of anoxæmia also had a tendency to increase the size of the vessels, but the effect was comparatively slight compared with that of carbon dioxide. Normally an increase in the oxygen content of the blood resulted in a very slight decrease in the diameter of the arteries. The influence of carbon dioxide, however, almost completely obscured that of oxygen. These workers also made the important observation that a dilatation of the vessels was more readily produced than a constriction. When the composition of the respired gas was altered, respiration was affected before either the systemic arterial blood-pressure or the size of the pial arteries.

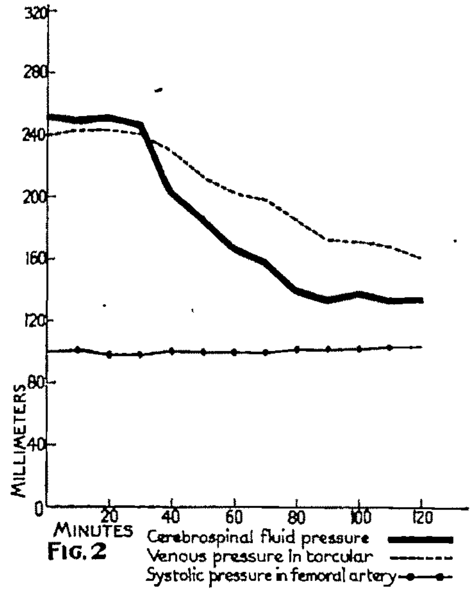

FIG. 2

FIG. 2.—The effect of continuous anæsthesia on the intracranial pressures of an animal in which the external jugular veins have been occluded for twenty-four hours. The pressure of the cerebrospinal fluid and the torcular venous pressure are recorded in millimetres of normal saline solution, that in the femoral artery in millimetres of mercury.

It must be admitted that this explanation of the high intracranial pressures in the survival experiments is mainly speculative. If, however, it is correct, the intracranial pressures should be found to fall considerably after complete anæsthesia has been achieved and the administration of the ether is maintained at a constant rate. The cerebrospinal fluid pressure, the torcular venous pressure and the arterial pressure in the femoral artery were now recorded in a number of dogs in which the external jugular veins had been occluded twenty-four hours earlier. The anæsthesia was maintained and the experiments were continued for several hours. By the end of the first hour the cerebrospinal fluid pressure had usually attained normal levels. A fall also occurred in the venous pressure in the torcular, but it was not so rapid or so complete, and at the end of the second hour it was higher than that of the cerebrospinal fluid. Throughout the experiments the arterial pressure in the femoral artery remained steady. A typical experiment is illustrated in fig. 2. The pressure changes in these experiments are identical with those observed in the acute experiments, except for a slightly longer period required for the pressure of the cerebrospinal fluid to return to normal levels. Now it is known that the raised pressure of the cerebrospinal fluid in the acute experiments is directly dependent on the raised intracranial venous pressure. It would seem reasonable, therefore, to conclude that the raised pressure of the cerebrospinal fluid in the recovery experiments has a similar origin.

The maximum duration of the acute experiments was three hours; at the end of this period the pressure of the cerebrospinal fluid was at a normal level, and although the venous pressure in the torcular was considerably reduced it was still somewhat higher than its original level. It has been suggested that the raised intracranial pressures in the experiments with a twenty-four hours recovery period were due either to an extra strain imposed on the intracranial venous circulation during the active recovery period, or to the cerebral congestion which occurs during the initial stages of the ether anæsthesia. If the latter view be correct it might be expected that the intracranial pressures would be found to be high even after a recovery period as short as one or two hours. In order to test this possibility the external jugular veins were occluded in two dogs. The animals were then allowed to recover from the anæsthetic and an hour and a half later they were again anæsthetized and a record taken of the intracranial pressures. It will be observed from Table IV that the pressures were of the same order as those found in the experiments with a more prolonged recovery period. The cerebrospinal fluid pressure and the torcular venous pressure also resemble in their relative heights the pressures found immediately after occlusion of the external jugular veins. This may perhaps indicate that the pressures have only just been raised. On maintaining the anæsthesia the cerebrospinal fluid pressure was found to have returned to normal levels after about an hour, although at that time the venous pressure was still higher than the normal. Although these experiments suggest very strongly that the raised intracranial pressures in the experiments with a recovery period were caused by the venous congestion which occurred during the initial stages of the ether anæsthesia, it must nevertheless be admitted that the experiments do not exclude the possibility that the pressures may be higher than normal during the period of recovery. No method is yet available by which the intracranial pressures can be recorded in the conscious animal.

TABLE IV.

Dog No.	Cerebrospinal fluid	Torcular venous	Femoral artery
1	(*a*) 220	280	115
	(*b*) 180	145	120
2	(*a*) 210	205	95
	(*b*) 185	170	95

The cerebrospinal fluid pressure, the torcular venous pressure and the arterial pressure in the femoral artery in two dogs in which the external jugular veins have been occluded. The animals were allowed to recover from the anæsthetic as soon as the vessels had been occluded and one and a half hours later they were again anæsthetized and a continuous record taken of the intracranial pressures.

(*a*) The pressure levels after complete anæsthesia had been attained.

(*b*) The pressure levels after anæsthesia had been maintained for one hour. The pressure of the cerebrospinal fluid and the torcular venous pressure are recorded in millimetres of normal saline solution, that in the femoral artery in millimetres of mercury.

It is noteworthy that it has been unnecessary to postulate an increased formation of cerebrospinal fluid in order to account for any of the phenomena associated with a prolonged occlusion of the external jugular veins.

SUMMARY.

(1) The intracranial pressures were found to be raised in animals in which the external jugular veins had been ligated for twenty-four hours. A careful examination after death of the brains and their coverings failed to reveal any cause for the high pressures.

(2) A study was made of the effect of changes in the pressure of the cerebrospinal fluid on the venous pressure in the torcular in animals in which the external jugular veins had been occluded. Changes in the pressure of the cerebrospinal fluid were found to be accompanied by changes in the same direction, although to a lesser degree, in the venous pressure at the torcular.

(3) An increased formation of cerebrospinal fluid was not, however, considered to be the cause of the raised pressures in the animals in

which the external jugular veins had been occluded for twenty-four hours. Experiments are described which suggest very strongly that the raised pressure of the cerebrospinal fluid was directly dependent on the raised intracranial venous pressure. It was also considered probable that the intracranial venous pressure had been raised during the initial stages of the ether anæsthesia.

REFERENCES.

[1] Becht, F. C. *Amer. Journ. Phys.*, 1920, **51**, 1.
[2] Bedford, T. H. B. *Brain*, 1934, **57**, 1.
[3] *Idem.* *Ibid.*, 1935, **58**, 427.
[4] Eyster, J. A. E. *Journ. Exper. Med.*, 1906, **8**, 565.
[5] Masserman, J. H., and Schaller, W. F. *Arch. Neur. and Psych.*, 1933, **30**, 107.
[6] Masserman, J. H. *Ibid.*, 1934, **32**, 523.
[7] Ossipow, V. P. *Deutsch. Ztschr. Nervenh.*, 1901, **19**, 350.
[8] Weed, L. H., and Hughson, W. *Amer. Journ. Phys.*, 1921-22, **58**, 101.
[9] Weed, L. H., and Flexner, L. B. *Ibid.*, 1933, **105**, 266.
[10] Wolff, H. G., and Lennox, W. G. *Arch. Neurol. and Psych.*, 1930, **23**, 1097.

PRIMARY TUMOURS OF THE ROOT OF THE FIFTH CRANIAL NERVE: THEIR DISTINCTION FROM TUMOURS OF THE GASSERIAN GANGLION.[1]

BY HUGO KRAYENBÜHL (ZURICH).

TUMOURS of the 5th nerve and its ganglion were formerly so rarely recognized that they were regarded as pathological curiosities, and their symptomatology was poorly defined. With the development of interest in neurosurgery during the last two decades, an increasing number of these tumours has been reported in the literature, and the possibility of successful radical treatment has become apparent. Hitherto case reports have been concerned for the most part with primary and secondary tumours of the Gasserian ganglion, and little is known of the tumours that arise in the retro-ganglionic root of the nerve.

In this paper it is proposed to report two cases of tumour arising from the nerve root, and to show by an analysis of the primary tumours reported in the literature that there is considerable difference between the clinical picture of tumours of the ganglion and that of tumours of the nerve behind the ganglion. The clinical distinction is important because the method of operative approach should differ radically in the two groups of cases. Few attempts have been made as yet to remove retro-ganglionic tumours, doubtless because the clinical picture produced by the tumour is insufficiently known.

Case 1.—*Neurofibroma of left 5th nerve. Three years' history of cerebello-pontine angle disturbances. Lumbar puncture. Rapid exitus.*

History.—J. D., a lorry driver, aged 55, was admitted to the London Hospital under the care of Dr. Russell Brain on April 6, 1935. He had enjoyed good health until three years before admission, when he began to have in the mornings shooting pains in the left side of the head. These started in the left temple and spread to the occiput. As time went on the pain became more severe and continuous, and he lost his employment. One year before admission he began to stagger to the right and to suffer from attacks of giddiness, which increased in severity and frequency. For two to three months he had noticed that the sight of the left eye was failing, that his teeth and gums on the left side felt numb, and this was followed by weakness of the left side of the face with difficulty in mastication, swallowing and speaking. He complained also that all foods tasted alike. He had become deaf in the left ear and had a feeling of numbness and weakness of the right hand, and his memory had become poor.

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Examination.—The positive signs were as follows: Bilateral anosmia. Bilateral papillœdema with severe impairment of vision. Lateral and upward nystagmus. Absence of both corneal reflexes. Anæsthesia and analgesia of the left side of the face, complete over the ophthalmic division and partial over the maxillary and mandibular divisions. Normal power in masticatory muscles. Severe upper and lower facial weakness on left side with constant dribbling of saliva from the left corner of the mouth. Deafness in the left ear. Hypotonia of all limbs and slight weakness of the right upper limb. Absence of all abdominal reflexes. Extensor plantar response on the left side.

X-rays showed no signs of increased intracranial pressure, but the dorsum sellæ and posterior clinoid processes were eroded. The cerebrospinal fluid showed no excess of white cells; the total protein was raised to 110 mgm. per cent. A few hours after lumbar puncture the patient became comatose; his temperature rose to 109° F., and he died. A clinical diagnosis of left acoustic neurinoma had been made.

Necropsy.—(P.M. 152, 1935). Examination was limited to the head. In the brain there was slight flattening and broadening of all convolutions of the anterior three-quarters of the convexities; slight downward projection of the gyrus rectus on each side; very slight foraminal herniation of the left cerebellar tonsil, which was displaced slightly to the right and forwards against the medulla. There was considerable whitish opacity of the leptomeninges over the cerebral convexities.

In the left cerebello-pontine angle was a smooth, firm, lobulated, greyish-white translucent tumour, 4·2 by 2·6 cm., compressing the left side of the pons and projecting backwards into the left cerebellar lobe (fig. 1). Medially it was in contact with the basilar artery throughout the greater part of its course. Caudally it extended down to the left 9th, 10th and 11th nerves, and laterally it was in contact with the petrous bone, but not attached to it, and the porus acusticus was normal. Rostrally it extended forwards through the dural opening into the cave of Meckel, where it formed a mass (2·2 by 1·8 by 1·2 cm.) in the position of the Gasserian ganglion (fig. 1 E), which indented the underlying bone.

The left 5th nerve was only found after the tumour had been tilted from its bed (fig. 1 B, C, D). In the proximal 1 cm. of its course it lay on the medial and dorsal aspect of the tumour, flattened betweeen the pons and the tumour. Then passing distally it divided into two flattened semi-transparent bands, 0·1 by 0·2 cm. wide, which entered the capsule of the tumour and then spread out into numerous ill-defined bundles. These bundles, in places difficult to distinguish from thicker parts of the capsule, ran for varying lengths on the dorsal surface of the tumour and then disappeared into its substance. At the level of the caudal end of the cave of Meckel no nerve-fibres could be seen on the surface of the tumour. In the cave of Meckel no trace of normal Gasserian ganglion could be detected, but only tumour (fig. 1 E). At the rostral end of the tumour all three divisions of the trigeminal nerve could be found, the third and second divisions possessing a normal appearance while the first division was small and flattened.

The left 4th nerve lay immediately cephalic to the apex of the growth. The left 6th nerve ran from its origin transversely across the ventral aspect of the tumour. The left 7th and 8th nerves emerged between the ventral surface of the cerebellum and the adjacent ventral and outer surface of the tumour (fig. 1 A).

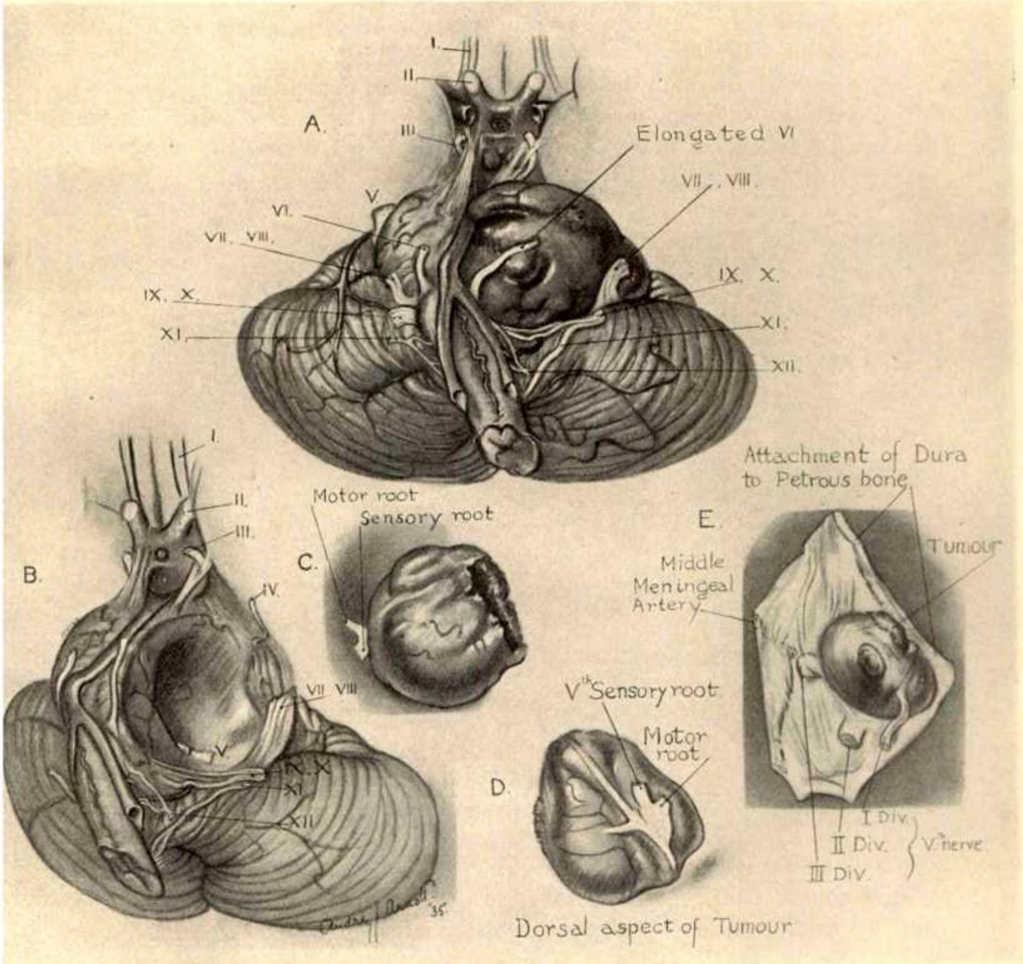

FIG. 1.—*Case* 1. Neurofibroma of the left 5th cranial nerve.

Sections through the tumour showed it to be composed of numerous cysts up to 1·3 cm. in diameter, and soft, glistening, translucent, grey tissue. The centre was occupied by large areas (about 2·3 cm. in diameter) of recent hæmorrhage, the greater part of which lay within cystic spaces. The part of the tumour adjacent to the pons was of a somewhat firmer consistency than the rest. In the cave of Meckel the tumour was firm, and pearly grey with numerous central cystic spaces up to 0·6 by 0·4 cm., and showed to the naked eye no traces of nerve-fibres or ganglion.

Microscopic examination.—Two sections were taken from the tumour in the posterior fossa, one of its rostral portion and the adjacent border of the pons, and the other of a portion with the flattened 5th nerve root attached to it. Two coronal sections were also taken of the tumour in the region of the left Gasserian ganglion, one through its greatest thickness and the other through its rostral end to include the three divisions of the trigeminal nerve.

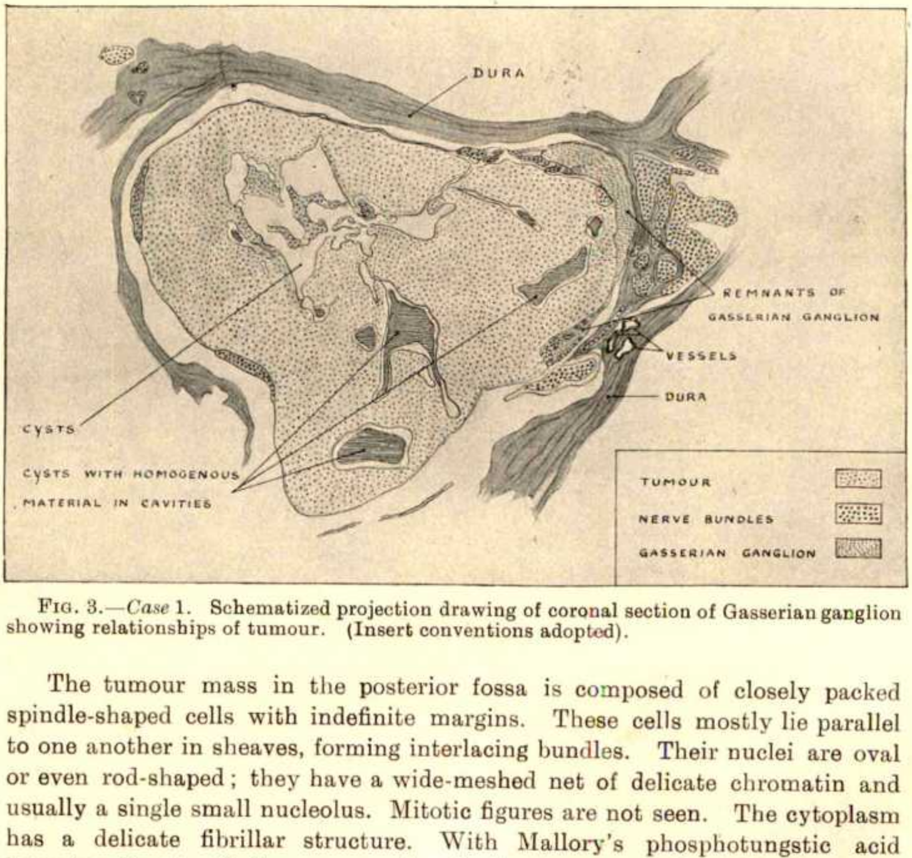
DURA
REMNANTS OF GASSERIAN GANGLION
VESSELS
DURA
CYSTS
CYSTS WITH HOMOGENOUS MATERIAL IN CAVITIES
TUMOUR
NERVE BUNDLES
GASSERIAN GANGLION

FIG. 3.—*Case* 1. Schematized projection drawing of coronal section of Gasserian ganglion showing relationships of tumour. (Insert conventions adopted).

The tumour mass in the posterior fossa is composed of closely packed spindle-shaped cells with indefinite margins. These cells mostly lie parallel to one another in sheaves, forming interlacing bundles. Their nuclei are oval or even rod-shaped; they have a wide-meshed net of delicate chromatin and usually a single small nucleolus. Mitotic figures are not seen. The cytoplasm has a delicate fibrillar structure. With Mallory's phosphotungstic acid hæmatoxylin the fibrils can occasionally be demonstrated. With Laidlaw's silver carbonate method for reticulum fibres many areas contain abundant very delicate parallel fibres which form interlacing bundles (Plate IV, fig. 2). Collagen fibres, as demonstrated with van Gieson's stain, are restricted to the walls of blood-vessels and their immediate neighbourhood. The tumour cells

PLATE IV.

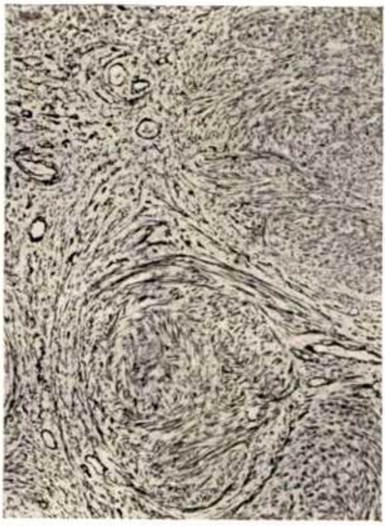

FIG. 2.

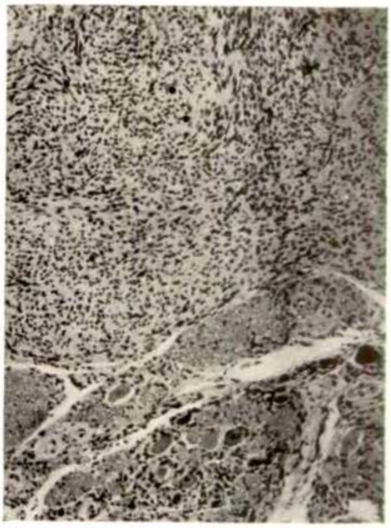

FIG. 4.

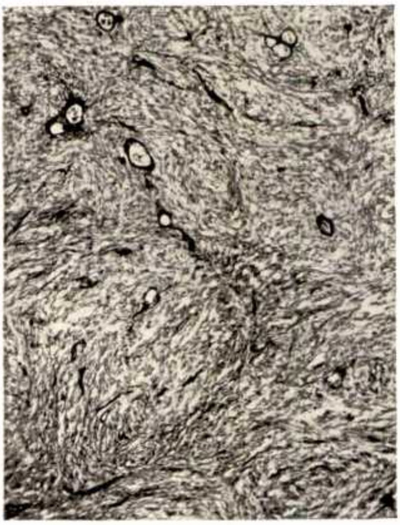

FIG. 6.

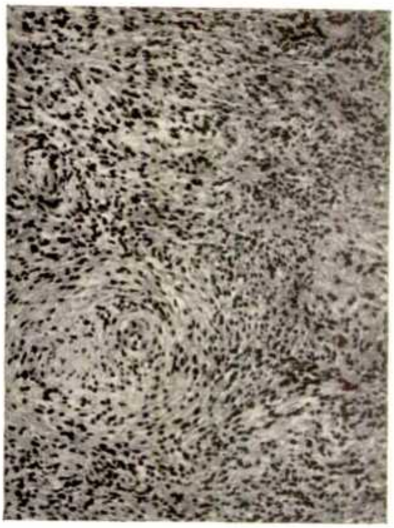

FIG. 7.

FIG. 2.—*Case* 1. Tumour in Gasserian ganglion showing reticulin fibrils. Laidlaw. × 100.

FIG. 4.—*Case* 1. Tumour in Gasserian ganglion, a portion of which is seen below. Hæmatoxylin and oosin. × 98.

FIG. 6.—*Case* 2. Tumour showing reticulin fibrils. Laidlaw. × 100.

FIG. 7.—*Case* 2. Tumour showing whorled arrangement of cells. Hæmatoxylin and eosin. × 118.

To illustrate paper by Hugo Krayenbühl.

sometimes form concentric nests about the blood-vessels or lie in whorls independent of a vascular core. The arrangement of the nuclei is occasionally suggestive of palisading, but this is nowhere pronounced.

In the deeper parts of the tumour the arrangement of the cells is frequently much less definite ; the fibrillar structure of the cytoplasm is absent and the spaces between the nuclei are occupied by fine anastomosing strands of cytoplasm. These areas merge into others where degeneration is clearly indicated by the loss of nuclei, and every transition can be demonstrated between this and cyst formation. In the walls of the cysts and elsewhere are occasional collections of macrophages containing iron pigment.

This part of the tumour, lying in the posterior fossa, is enclosed by a thin collagenous capsule derived from the leptomeninges. Nerve fibres are not seen inside the tumour, they are only present in the capsule.

Both sections through the Gasserian ganglion region show a central mass of tumour tissue continued forwards from the main tumour in the posterior fossa (fig. 3). It presents histological features similar to those that have already been described, except that fibrils were not demonstrated with phosphotungstic acid hæmatoxylin. Investing the tumour tissue is a layer of delicate interlacing collagenous fibres of variable thickness, the outer surface of which is coated with a single layer of greatly flattened cells. In this layer are incorporated the Gasserian ganglion and bundles of nerve-fibres. The Gasserian ganglion forms a thin crescentic mass on the dorsal aspect, and its cells are of normal appearance and shape, except for a few degenerative changes (Plate IV, fig. 4). The nerve-fibres, which are myelinated, are distributed all over the capsule of this part of the tumour either as well-defined bundles surrounded by an endothelial capsule, or as isolated fibres. A few individual fibres pass into the adjacent tumour, but they are confined to its superficial parts. The tumour does not invade the dura of the cave of Meckel, but is separated from it by a thin space lined by a single layer of greatly flattened cells which obviously represents the subdural space.

Comment.—The anatomical and histological features of this tumour leave little doubt that it is a neurofibroma of the trigeminal nerve. Histologically it resembles the corresponding tumours that arise on the 8th nerve, both in the morphology of its cells, the abundant though focal production of reticulum fibres, and in its tendency to undergo cystic degeneration. The main bulk of the tumour was situated in the cerebellopontine angle, the 7th and 8th nerves formed a large bundle that was not connected with the tumour, and the fibres of the 5th nerve were in their proximal part spread out in the capsule and in their distal part lost in the substance of the tumour. The tumour was invested by the leptomeninges and not attached to the dura.

The rostral portion of the tumour occupied the cave of Meckel, but there was no evidence that the tumour arose in the Gasserian ganglion, since histological examination showed flattened but otherwise normal components of the ganglion spread out over the dorsal surface of the tumour. An identical relationship of the ganglion to a tumour of the trigeminal nerve has been demonstrated in a recent example of v. Recklinghausen's central neurofibromatosis (P.M. 316, 1935), in which diffuse tumours were present on both trigeminal nerves as well as upon many other cranial and spinal nerve roots. It may be presumed, therefore, that the tumour in Case 1 arose in the sheath of the trigeminal nerve behind the ganglion.

This case had not been completely investigated, especially as regards hearing and vestibular functions, at the time when the unfortunate catastrophe occurred following lumbar puncture. However, even with full investigations it is doubtful whether the provisional diagnosis of acoustic neurinoma would have changed, for most of the clinical features of the case fitted closely the clinical picture of acoustic neurinoma. Although the illness was of three years' duration numbness in the trigeminal area was only complained of three months before death. And pain in the face was entirely absent; this is characteristic of most tumours of the trigeminal root.

Most of the cases reported in the literature could not be distinguished with certainty from acoustic neurinoma, but the following case is representative of a small group in which differential diagnosis is possible by virtue of severe primary trigeminal symptoms and other features.

Case 2.—*Neurofibroma of right trigeminal nerve. Six years' illness of headache, sensory disturbance in right side of face, staggering, deafness, mental deterioration, &c. Death.*

History.—W. P., a male dust destructor worker, aged 55, referred by Dr. Flood, was first admitted to the London Hospital on June 27, 1931, on account of headaches and attacks of unconsciousness. From the age of 2, he had had a squint of the right eye, attributed to a fall on the head. In July, 1926, his right testicle had been removed for swelling, associated with hæmaturia.

In January, 1927, he began to suffer from short attacks of headache, for the most part in the right temporal region, but sometimes extending to the neck and then accompanied by stiffness. This headache was not frequent at first, and he continued at work. But gradually it became more intense, and the attacks, which lasted from half to one minute, occurred a dozen times a day. From the onset of the illness he had also had at times a feeling of numbness on the right side of the forehead and right side of the face, as though it were stiff and starched. In the same part of the face he had at times some pain, but had never considered this symptom as a major part of his complaint.

In 1929 his vision began to fail. He staggered to the left when walking, began to drop things held in the left hand and his left foot was sometimes observed to twitch during the night.

In November, 1929, he was admitted to Charing Cross Hospital under the care of Dr. Gordon Holmes, to whom we are indebted for the following information: The right eye was almost immobile, drawn outward and slightly down; the visual fields were diminished from the periphery. Analgesia was found on the right side of the face, and weakness of the right masseter muscle. Deafness was bilateral, more marked on the right than on the left. There was a diminution of power and co-ordination in the left upper and lower limbs and the outstretched left upper limb was not well maintained. The left knee-jerk was brisker than the right and the left plantar response was extensor. Protein in the cerebrospinal fluid was slightly raised, being 0·050 per cent., with a very faint excess of globulin, and one white cell per c.mm. Dr. Holmes made a diagnosis of a very slowly progressing cerebral tumour involving the right 5th nerve and considered that an operation was inadvisable.

The patient returned to work, but had to give it up a few weeks later because of disturbance of gait. He was walking like an intoxicated man and dragging the left foot. Though at times his balance seemed to improve slightly, he could not walk without support. When bending forwards he often experienced a feeling of giddiness, but external objects did not appear to rotate. Trembling of both hands, worse on the left side than on the right, also developed at this stage.

In September, 1930, the patient had an attack of stupor which lasted nearly two months; he did not seem to know anybody or to realize that he was in bed or what was being done for him; he would answer if spoken to, but never spoke voluntarily; he was incontinent of urine and fæces. He gradually recovered from this attack, but from that time his memory failed progressively, his intelligence deteriorated, and his emotional reactions gradually became excessive. At this stage he also began to notice that he could not masticate on the right side. He thought, too, that there was a loss of sensation in his mouth. Tinnitus was present at times, but never severe.

Examination. June, 1931.—The patient was a man of low intelligence and deficient memory. Smell was diminished at both nostrils; both optic discs were flat; there was an external squint and amblyopia of the right eye; upward movement of the left eye was diminished. Visual acuity: $\frac{2}{24}$ on the right, $\frac{6}{18}$ on the left side. The right corneal reflex was absent; there was very slight relative anæsthesia to cotton-wool on the right side of the face, relative analgesia in the right ophthalmic division and slight deviation of the jaw to the right.

Other symptoms were slight left lower facial weakness; bilateral incomplete deafness, more marked on the right than on the left; slight flaccid paresis of the left upper and lower limbs; increased tendon-jerks and an extensor plantar response on the left side; gait slow, on a wide base, with a tendency to fall to the right; normal sensibility to posture, cotton wool and pin-prick.

X-rays showed a fairly thin vault without increase of convolutional markings. The sella turcica was of normal size, but the posterior clinoid processes appeared to be eroded. Ventriculography showed bilateral symmetrical hydrocephalus of moderate degree. No surgical treatment was undertaken, because, from the evidence of pressure upon the right cerebral peduncle, it was considered that the lesion was inaccessible.

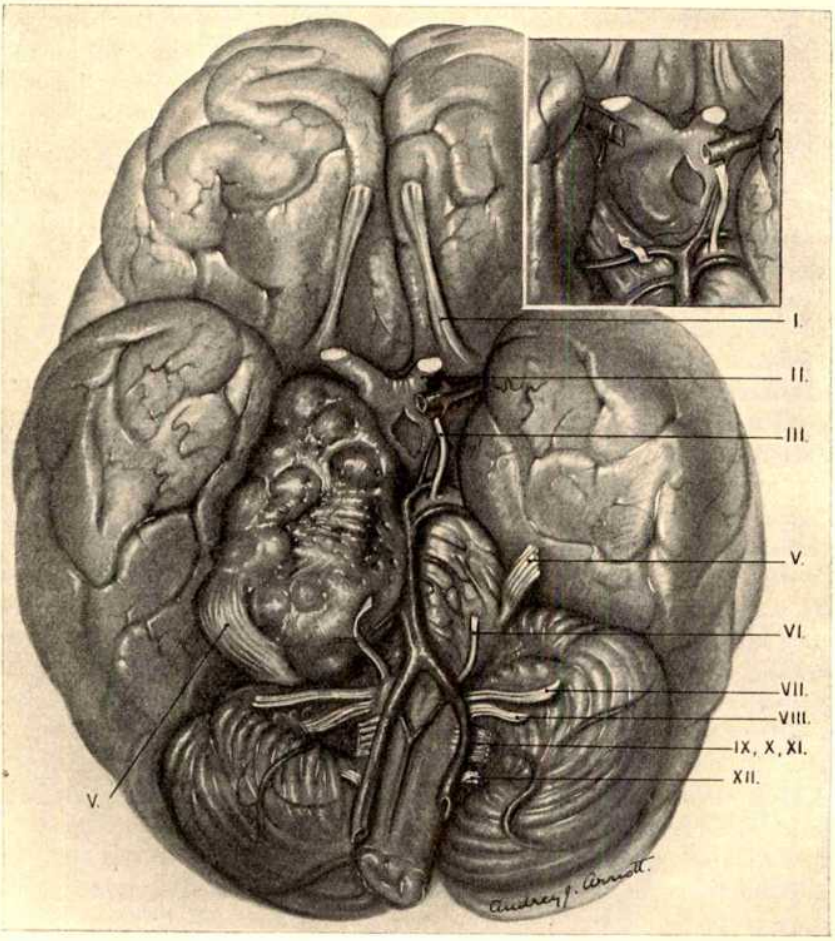

FIG. 5.—*Case* 2. Neurofibroma of the right 5th cranial nerve.

Subsequent course.—After his discharge on July 11, 1931, the patient grew gradually worse, and was in bed at home most of the time. He was readmitted to hospital in February, 1933. His mental condition had further deteriorated; he was incontinent of urine, partially disorientated and very drowsy. There was still no papillœdema, the right corneal reflex was greatly diminished and there was analgesia over the right forehead and over the right side of the nose, but the sensibility on the lower part of the face was still within normal limits. All limbs were spastic and there was now a bilateral extensor response. The patient went home again, and a few weeks later lapsed into coma and died.

Necropsy. (P.M. 605, 1930, Appendix).—The brain was obtained through the kindness of Dr. Deacon. When it was removed from the skull a large, greyish white, smooth, encapsulated, soft tumour was disclosed situated in the posterior fossa, extending through the tentorium into the middle fossa, where it appeared to replace the right trigeminal nerve and the Gasserian ganglion. Unfortunately the middle fossa extension of the tumour was not removed completely, but a small portion of it was taken for section.

Examination of the brain after fixation.—A tumour measuring 7·0 by 4·0 by 2·5 cm. lay in the right cerebellopontine angle and extended forwards into the cave of Meckel and beneath the floor of the third ventricle (fig. 5). It was embedded in the ventral surface of the right side of the floor of the third ventricle. Anteriorly and laterally the dorsal surface of the tumour indented the ventral surface of the hippocampal gyrus which was flattened between the tumour and the right cerebral peduncle. Caudally and laterally the growth lay in contact with the right middle cerebellar peduncle and excavated slightly the anterior end of the right anterior crescentic lobule.

The right 7th to 12th cranial nerves lay on the caudal side of the tumour and were not in contact with it, at any rate, not in the proximal part of their course. The right 7th nerve was flattened to a translucent grey strand less than 0·05 cm. wide which passed over the ventral surface of the tumour.

At its junction with the pons the right 5th nerve was separated into two parts by the tumour; the greater part of it passed over the ventrolateral aspect of the tumour as a broad splayed-out strand of fibres 0·7 cm. wide, which is shown in fig. 5; the smaller and less flattened part crossed the dorsolateral aspect of the tumour. At its origin the nerve was distinct from the tumour, but in its more distal part it was spread out diffusely and incorporated in the capsule of the tumour.

The right 3rd and 4th nerves lay on the dorsal aspect of the tumour. From its origin the right 3rd nerve passed in a caudal direction to loop around the posterior cerebral artery, being thinned at that point (fig. 5). It then came forward over the dorsal-cephalic surface of the tumour, fairly closely attached to its capsule over a length of 2·5 cm. In this part of its course it was flattened almost to translucency and to a width of 0·6 cm. by tumour nodules that projected into it. The posterior half of the right optic tract was flattened and displaced outwards by the tumour immediately below it. The tumour did not reach the optic chiasm.

Coronal sections through the brain showed a moderate degree of symmetrical dilatation of the lateral ventricles and a considerable dilatation of the third ventricle.

The tumour was sharply circumscribed by a smooth, and in places, glistening white and greyish-white and yellowish-white translucent tissue in which were several empty cysts up to 2·5 cm. in diameter. These cysts were lined for the most part with smooth glistening tissue and crossed by white septa or fine trabeculæ.

Microscopic examination.—Sections were taken through the tumour of the posterior fossa and the adjacent pons and through fragments of the tumour of the middle fossa.

The tumour in the posterior fossa is closely apposed to the pons and the leptomeninges here form the capsule of the tumour. They are infiltrated with lymphocytes and macrophages, many of which contain iron pigment. There is no invasion of the pons by tumour. Histologically the tumour itself is identical in appearance with the one described in the preceding case (Plate IV, figs. 6 and 7), except in the following particulars. The amount of cystic degeneration in the interior of the tumour is greater, the cysts being both larger and more numerous. There is a correspondingly greater amount of degeneration in the adjoining tumour tissue and throughout large areas the cell nuclei have disappeared or have been replaced by collections of macrophages containing iron pigment. Small bundles of myelinated nerve fibres are present in different parts of the tumour, usually near the periphery. In two places these fibres run straight through the tumour and are accompanied by a few psammoma bodies.

The fragments taken from the middle fossa include a few collections of ganglion cells. These are surrounded by their capsular cells and appear normal. They are evidently derived from the Gasserian ganglion, but their precise relationship cannot be stated.

Comment.—This tumour resembled closely in its macroscopic and microscopic appearances the tumour in Case 1 and may, therefore, be classed as a neurofibroma. It is unfortunate that the middle fossa extension of the tumour was not removed completely at the necropsy, and that the precise relation of the tumour to the Gasserian ganglion is therefore not known. However, in the fragments from the middle fossa that were available ganglion and capsular cells were of normal appearance and it is reasonable to assume, therefore, that the tumour did not arise in the Gasserian ganglion. As in Case 1 the tumour probably took its origin from the distal part of the root. Whether it arose from the root behind or within the cave of Meckel it is impossible to say. In this connection, however, it may be noted that in the two cases of small "Schwannoma" reported in the literature (Alajouanine, de Martel, Oberling and Guillaume [1] and Alajouanine, Thurel and Guillaume [2]) the tumour lay on the nerve just behind the level of the apex of the petrous bone.

In the clinical course of our two cases the most striking feature is the inconspicuous character of the subjective trigeminal symptoms, and especially the complete or almost complete absence of pain. In Case 1 a feeling of numbness in the second and third divisional areas of the affected nerve came on only in the last three months of the illness. In Case 2 a feeling of numbness over all three divisional areas was present at times during the whole illness, but was overshadowed by other symptoms; pain in the face was felt at times but was never severe. On examination anæsthesia and analgesia were present in both cases and in one case the motor root was also slightly affected.

Analysis of the reported cases shows that absence of pain in primary tumours of the trigeminal root is by means unusual, and that this fact is in marked contradistinction to what happens in primary tumours of the Gasserian ganglion. I have been able to find in the literature 54 cases of primary tumour of the Gasserian ganglion or trigeminal root. From the pathological reports it is only possible in 29 cases to be certain as to the exact origin of the tumour, whether from the ganglion or from the root. In 26 cases the tumour arose from the ganglion. In 2 of them the clinical reports were incomplete [15, 42], but in every one of the remaining 24 severe continuous pain of the face of an aching, throbbing or burning character was the initial symptom and persisted throughout the whole illness. In the 3 cases in which the tumour clearly arose from the trigeminal root, pain in the face was absent during the whole course of the illness in two (Glaser [7], Alajouanine, Thurel and Guillaume [2]), and was of only moderate degree in the third (Alajouanine, de Martel, Oberling and Guillaume [1]).

If the 54 cases from the literature are studied from the clinical standpoint it is possible from the order in which symptoms appeared to form an opinion in every case as to the probable origin of the tumour in the middle or posterior fossa. In 39 cases with an onset pointing to the middle fossa all had severe facial pain. In 13 of these cases the tumour extended into the posterior fossa, and pain remained constant except in the cases of Dew [20] and Nowotny and Uiberall [34], where it disappeared after six months and two years respectively. The 15 cases with an onset pointing to the posterior fossa (as indicated by lower cranial nerve palsies, cerebellar or cerebral peduncle signs) had marked pain in 2 cases, slight pain in 5 cases and none in 8 cases.

The outstanding fact is that in 56 cases of tumour of the Gasserian ganglion and the trigeminal root, if the two cases of this paper are included, there were 15 cases in which facial pain was slight or absent. From this analysis of the literature it is probable that pain occurs when the ganglion is primarily involved and is usually absent when the tumour begins on the trigeminal root. It is not surprising that when primary root tumours spread to the ganglion pain does not occur; for by that time conduction of impulses centrally is impaired by destruction of fibres in the root. This explanation is in accord with the view of Pierre Marie when he reported his case of root tumour [11].

These trigeminal root tumours provide a variety of initial symptoms. A closer study of the 2 cases reported in this paper and the 15 cases from the literature reveals a definite symptomatology of cerebellopontine angle involvement, 2 cases presenting vertigo, 2 tinnitus, 3 tinnitus and deafness, 2 unsteadiness in walking associated with vertigo, and 1 facial spasm. In our own 2 cases unilateral headache and in another case failure of vision was the first symptom. Only 2 cases were initiated by a sudden facial numbness, and in 1 case a feeling of coldness in the face associated with toothache on the same side was the first symptom. The case reported by Alajouanine, de Martel, Oberling and Guillaume is the only one in this series in which facial pain was present from the very beginning.

During the further course of the illness trigeminal symptoms became more conspicuous, but they are by no means so severe as one might have expected. In 14 cases subjective trigeminal symptoms were present: the feeling of numbness, coldness and tingling was a prominent symptom from periods varying from several weeks to several months in 10 cases, and was in 5 instances at times associated with slight facial pain. Four cases presented at times some pain, but it was severe and constant in only two instances (Shelden [14], Alajouanine, de Martel, Oberling and Guillaume [1]). In 3 cases, each of them thoroughly studied, no subjective trigeminal symptoms were recorded at all (3*a*, 3*b*, 9).

The objective evidence of trigeminal affection gives a picture very different from that suggested by the subjective symptoms, as sensory loss was marked in the whole series. In one case (Petrina and Klebs [13]) the physical examination is incomplete. Of the remaining 16 cases, 10 had either complete or relative anæsthesia and analgesia over one entire side of the face, 2 were affected in the first and 2 in the second divisional area alone, and in 1 case the first and second, and in another the second and third branch were involved. The corneal reflex was diminished or absent on the side of the tumour in 10 cases and was impaired on both sides in 2 cases. Ulceration of the cornea is reported twice, and the motor branch showed weakness and partial atrophy of the masticatory muscles in 7 cases.

Deafness is as a rule one of the earliest symptoms in the course of these tumours, and it has been reported three times as an initial symptom. Generally its onset is gradual, but it steadily increases until it is almost complete. It is reported in 13 out of the 17 cases, and twice, as in Case 2, it was bilateral, but much more marked on the side of the tumour. Caloric tests were done in 5 cases and showed an impairment of the vestibular function on the side of the tumour. Tinnitus has been recorded only five times, and was then present from the very beginning. Facial weakness was noticed in half the cases, and involvement of the 9th, 10th, 11th, and 12th cranial nerves was reported in 11 cases. Staggering gait was present ten times, and was often associated with vertigo and homolateral ataxia.

Evidence of involvement of the cerebral peduncles is of special interest in the diagnosis of these tumours, as shown in our Case 2. In 4 cases contralateral pyramidal signs were reported, and in 3 cases they occurred on the homolateral side.

Intracranial pressure is, as a rule, only moderately raised in these tumours. Headache was present in 9 cases and was usually not severe. It reached an intense degree only in our 2 cases, where it was strictly unilateral. Moderate papillœdema and some optic atrophy was noticed in 25 per cent. of the cases, and failure of vision occurred five times. Vomiting was reported only twice. From these facts it is probable that the rate of growth of these tumours is slower than that of acoustic tumours.

The analysis of the symptoms of the reported cases shows that the diagnosis of a trigeminal root tumour is by no means easy. The main difficulty is to distinguish between a tumour of the trigeminal root and a tumour of the acoustic nerve. In acoustic tumours the degree of deafness and vestibular loss is usually greater than the degree of trigeminal sensory loss on the side of the lesion, but not invariably so. In trigeminal root tumours, however, the degree of objective trigeminal sensory loss is not always greater than the degree of deafness, so far as can be judged from the information at present available. Consequently there are many cases in which a precise differential diagnosis could not be made. However, in certain cases forward extension of a trigeminal root tumour at a relatively early stage of the illness will give distinctive signs. Thus, in our Case 2 the early sensory and motor involvement of the trigeminal nerve, coupled with evidence of pressure on the adjacent cerebral peduncle, gave a clinical picture from which the correct diagnosis was made. A further aid to diagnosis of trigeminal root tumours is derived from the fact that these tumours, in their almost invariable extension forwards into the middle fossa, often produce ocular palsies. These occurred seven times in the 17 reported cases, and were described as 3rd, 4th and 6th nerve palsies. In two instances also a Horner-Claude Bernard syndrome was noticed as a result of pressure by the tumour on the sympathetic fibres of the internal carotid plexus.

Help may sometimes be obtained from radiographic examination of the skull. In most of the cases the reported radiological investigations were negative, but in the case reported by Nowotny and Uiberall [12] X-rays showed erosion of the apex of the petrous bone and of the floor of the middle fossa in the region of the cave of Meckel. Similar appearances in the apex of the petrous bone may sometimes be seen in acoustic tumours. Dilatation of the porus acusticus indicates an acoustic tumour, but its absence is of no diagnostic significance. For operation to remove a tumour from the cerebello-pontine angle the importance of foreknowledge that there is an extension into the cave of Meckel needs no emphasis. Operation has been undertaken in only six cases. In two cases the tumour was completely and successfully removed by de Martel [1] and Guillaume [2], one by the middle fossa approach with division of the tentorium along the crest of the petrous bone, and one by the posterior approach. Both were small tumours. In the cases of Cushing [4] and Shelden [14] the removal of the tumour by the temporal approach was incomplete as the tumour occupied largely both the posterior and middle fossa. The other two reported cases [5, 12] died from the operation.

SUMMARY.

(1) Two cases of primary neurofibroma of the trigeminal nerve-root are described.

(2) Fifty-four cases of primary tumours of the trigeminal root and Gasserian ganglion reported in the literature are analysed.

(3) From this analysis there appears to be a distinction between the clinical picture of Gasserian ganglion tumours and that of trigeminal root-tumours. In Gasserian ganglion tumours continuous facial pain is the main symptom. In trigeminal root tumours facial pain is usually slight or absent and the clinical picture is one of cerebellopontine angle disorder.

(4) The symptomatology and diagnosis of trigeminal root tumours is discussed.

I desire to thank Mr. Hugh Cairns for his help in the preparation of this paper and for allowing me free access to all his material. I am also greatly indebted to Dr. Dorothy Russell for assistance in preparing the pathological section of this paper and to Dr. Russell Brain for permission to use the clinical record of Case 1.

BIBLIOGRAPHY.

A.—Primary Tumours of the Trigeminal Root.

[1] Alajouanine, Th., de Martel, Th., Oberling and Guillaume, J. *Rev. Neurol.*, 1930, **54**, 1250.
[2] Alajouanine, Th., Thurel, R., and Guillaume, J. *Ibid.*, 1935, **63**, 897.
[3] Altmann, F. *Beitr. z. path. Anat. u. z. allg. Path.*, 1928, **80**, 361 (2 cases).
[4] Cushing, H. *Amer. Journ. Med. Sci.*, 1920, **160**, 157.
[5] Giani. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1908, **19**, 452.
[6] Gjertz and Hellerstrom. *Acta Med. Scand.*, 1928, **68**, H. 1-2.
[7] Glaser, M. A. *Annals of Surgery*, 1935, **101**, 146.
[8] Hagelstam. *Deutsch. Zeitschr. f. Nervenheilk.*, 1898, **13**, 205.
[9] Hellsten, M. *Ibid.*, 1914, **52**, 290.
[10] Homen. *Neurol. Centralblatt*, 1890, **9**, 385.
[11] Marie, Pierre, Bouttier, H., and Bertrand, J., *Rev. Neurol.*, 1920, **10**, 977.
[12] Nowotny, K., and Uiberall, H. *Zeitschr. f. d. ges. Neurol. und Psychiatr.*, 1934, **150**, 75.
[13] Petrina and Klebs, E. *Prager Viertelj. f. prakt. Heilkde.*, 1877, 133 and 134.
[14] Shelden, W. D. *Journ. Amer. Med. Assoc.*, 1921, **77**, 700.

B.—Primary Tumours of the Gasserian Ganglion.

[15] Blessig. *St. Petersburger med. Zeitschr.*, 1866, **10**, 65.
[16] Bradley, G., and Walton-Smith, P. E. *Med. Journ. Australia*, 1931, **18**, 1931.
[17] Cohen, J. *Journ. Nerv. and Ment. Dis.*, 1933, **78**, 492.
[18] Cooper, M. J. *Amer. Journ. Med. Sci.*, 1933, **185**, 315 (3 cases).
[19] Dercum, F X., Keen, W. M., and Spiller, W. G. *Amer. Journ. Med. Assoc.*, 1900, **34**, 1026.
[20] Dew, H. R. *Australia and New Zealand Journ. Surg.*, 1933, **3**, 130.
[21] Frazier, Ch. H. *Amer. Journ. Med. Sci.*, 1918, **156**, 483 (3 cases).
[22] Gaines. *Med. Clinics of N. America*, 1929, **12**, 1245.
[23] Goodhart. *Trans. Path. Soc. Lond.*, 1886, **37**, 21 (2 cases).
[24] Hartmann, F. *Journ. f. Psychologie u. Neurol.*, 1905-6, **6** and **7**, 209 (2 cases).
[25] Hausch, V. *Münch. med. Wchnschr.*, 1886, **33**, 702.
[26] Hofmeister and Meyer. *Deutsche Zeitschr. f. Nervenheilk.*, 1906, **30**, 207.
[27] Krebs, M. E., Rappoport, F., and David, M. *Rev. Neurol.*, 1932, **58**, 700.
[28] Krepuska. *Monatschr. f. Ohrenhkde.*, 1898, **32**, 78.
[29] Krogius, A. *Rev. de Chir.*, 1896, **16**, 434.
[30] Learmonth, J. R., and Kernohan, J. W. *Brain*, 1930, **53**, 86.
[31] Little, T. E. *Dublin Journ. Med. Sci.*, 1873, **55**, 94.
[32] Marchand, F. *Festschr. f. Rindfleisch*, Leipzig, 1907, p. 265.
[33] Mixter, J., and Lund, Ch. C. *Arch. Neurol. and Psychiatr.*, 1936, **35**, 432.
[34] Nowotny, K., and Uiberall, H. *Zeitschr. f. d. ges. Neurol. and Psychiatr.*, 1934, **150**, 75 (2 cases).
[35] Parker, H. L. *Minnesota Med.*, 1924, **7**, 69.
[36] Rand, C. W. *Surg. Gyn. Obst.*, 1925, **40**, 49.
[37] Russell, E. C. *Journ. Amer. Med. Assoc.*, 1925, **84**, 413.

[38] Sachs, B., and Berg, A. A. *Berlin klin. Wchnschr.*, 1913, **50**, 1395.

[39] Sachs, E. *Annals of Surgery*, 1917, **66**, 152.

[40] Shelden, W. D. *Journ. Amer. Med. Assoc.*, 1921, **77**, 700 (2 cases).

[41] Smith, R. W. “A Treatise on the Pathological Diagnosis and Treatment of Neuroma.” Dublin, 1849.

[42] Söderbergh. *Nord. Med. Arkiv.*, 1909, Abt. II, H. 34.

[43] Spiller, W. *Amer. Journ. Med. Sci.*, 1908, **136**, 721.

[44] Stammers, F. A. R. *Brit. Journ. Surg.*, 1930, **18**, 125 (2 cases).

[45] Verger, H., and Grenier, H. *Rev. Neurol*, 1905, **10**, 704.

NEUROMYELITIS OPTICA.

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HISTORICALLY, it was Sir Clifford Allbutt [1] who, in 1870, first reported ophthalmoscopic signs associated with spinal cord disease. Using a relatively new instrument, the ophthalmoscope, he described blurring of the disc margins, slight hyperæmia, and atrophy of the disc in several cases of myelitis. He was followed in turn by Erb, Steffan, Chauval, Sequin, Noyes, Rumpf, Chisholm, Dreschfeld and Knapp. In 1889 Achard and Guinon reported the first clinico-pathological study of this disease. Then Eskridge, Drake-Brockman, Mahokian, Shanz, and Sharkey and Lawford each reported cases. Devic [2] summarized these cases in his classical "Thèse de Lyon" and this classical entity has, since then, often been referred to as "Devic's Syndrome." Reports appeared regularly thereafter in the literature of most countries and in 1927 Beck [3] made a careful review of seventy cases. Since then about forty additional cases have been reported.

This report includes the clinico-pathological studies of three cases and the clinical report of a fourth case of neuromyelitis optica. There are many cases in the literature, even to the present day, reported under this title which on analysis prove to be disseminated or diffuse sclerosis. It is intended in this report to indicate the reasons for setting apart this disease from acute disseminated and diffuse sclerosis and acute disseminated encephomyelitis, to reconsider its ætiology, and to discuss questions raised by Beck and others.

Devic called this syndrome "neuromyélite optique aiguë." Other synonyms which have appeared are acute disseminated myelitis, neuroptico-myelitis, neuromyelitis optica, diffuse myelitis, diffuse myelitis with optic neuritis, ophthalmoneuromyélite, neuropticomyélite aiguë and Devic's syndrome.

The ætiology is unknown. There are several different schools of thought. Milian, Lhermitte, Schaeffer and Horowitz considered it a virus disease and attempted to isolate the virus, but were unsuccessful. They made intracerebral and corneal scarification inoculations in dogs and monkeys with the cerebrospinal fluid of a case which they had observed. Redlich and Pette include this disease in disseminated encephalomyelitis and also believe it to be due to a filtrable virus. J. Dechaume, Von Bogaert and Vedel and Puech consider it part of the syndrome of epidemic encephalitis. Van Gehucten and Gaudissart include it in the myelitides, while Guillain and L. Michaux consider it a separate nosologic entity. In all countries there are many who consider it a form of acute disseminated sclerosis.

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REPORT OF CASES.

Case 1.—A. S., a female, aged 42, was admitted to the National Hospital, Queen Square, under Dr. Gordon Holmes on September 11, 1935. She was entirely well up to two months prior to admission when she developed marked asthenia and an aching pain, gradual in onset, down the inner aspect of both thighs and the backs of both legs. This pain spread up the back so that three weeks before admission it was present in the shoulders and neck; at that time she complained of impairment of vision in both eyes. The pain was gradually replaced by itching. The following week, her vision became worse, she became generally weak, especially in her right leg, and she now felt feverish. One week later she was admitted to the South London Hospital for Women, where examination revealed a temperature of 101° F., inequality of the pupils, the left being larger than the right, with visual acuity of $\frac{6}{60}$ in both eyes. There was rigidity of the neck. The abdominal reflexes were absent and she had bilateral extensor plantar responses. The cerebrospinal fluid was reported as being normal. At this time, urinary incontinence appeared and was followed by retention. Four days before admission her vision improved, but the following day it again became worse and she complained of photophobia. The next day she was completely blind.

On examination in the National Hospital, she lay helplessly in bed, breathing mainly with her accessory respiratory muscles. She appeared quiet and rather drowsy. She was totally blind, both optic discs being hyperæmic with blurring of the upper nasal edges. Her pupils were unequal, the left being larger than the right. There was no wasting or alteration in tone in the upper extremities, but paresis and a coarse tremor of both hands and arms were present. The lower intercostal muscles were moving poorly and she was unable to sit up. There was weakness in both lower extremities. Her abdominal reflexes could not be elicited. There was a bilateral extensor plantar response. She had analgesia to pin-prick up to the 6th dorsal segment, with a 6-in. band of hyperalgesia above this level. Cotton-wool and vibration were normally appreciated on the legs. Examination of the other systems gave negative results. The cerebrospinal fluid had a fine flocculent coagulum, 184 cells, of which 15 per cent. were polymorphonuclear leucocytes, and a total protein of 80 mgm. per cent. The Wassermann reaction and colloidal gold curve were negative.

The illness rapidly progressed so that on September 18 she was placed in a Drinker respirator because of difficulty in breathing. Death occurred the following day.

Post-mortem examination.—There was a slight erosion of the skin over the chin and sacrum and considerable lividity of the face and neck. The brain, spinal cord, optic nerves and posterior part of the retinæ were removed. These looked normal except for an area at about the 5th and 6th dorsal segments in the cord which was shrunken and more pink than other parts of the cord. The lungs, heart, stomach and intestines were healthy. There was some cloudy swelling of the liver and early septic changes in the spleen. The pelvis of the right kidney was dilated in its upper part and its wall was hæmorrhagic and inflamed. The bladder wall was intensely congested and contained blood-stained urine.

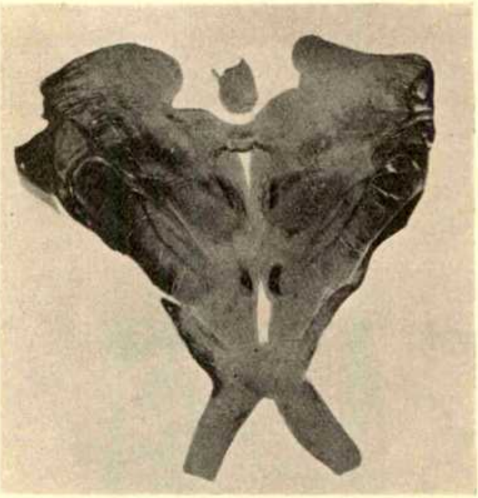

FIG. 1.—A. S. Section through optic nerves, chiasm, optic tracts and adjacent structures showing extensive demyelinization. Weigert-Pal counterstained with carmine.

Section from the frontal and occipital lobes, the basal ganglia, the optic nerves, chiasm, and tracts with the neighbouring diencephalic structures, the mesencephalon, pons, medulla and spinal cord were embedded in celloidin. Sections were stained by the Weigert-Pal method for myelin sheaths, the Gros-Bielschowsky method for axis cylinders, the aniline blue-orange G method for neuroglia fibres and cells, and by the Van Gieson, thionin blue and Perdrau methods.

In the white matter of the centrum ovale and in the basal ganglia, there was here and there a perivascular infiltration of lymphocytes and plasma cells but no other changes. A section through the optic nerves, chiasm and tracts and neighbouring hypothalamus and geniculate bodies showed the severity of the pathological process (fig. 1). These sections stained with Weigert-Pal, counterstained with carmine, showed a diffuse affection of the myelin sheaths, almost complete in extent, of both optic nerves and the chiasm. The tracts, although severely involved, were almost intact in their posterior portions. Gros-Bielschowsky stains of the optic nerves showed the axis-cylinders in a state of thickening, fragmentation or end-bulb formation, or completely destroyed (Plate V, fig. 2). Despite this degree of involvement, small islands of apparently intact myelin sheaths and axis-cylinders were seen in these areas. The perivascular infiltration was marked and contained lymphocytes, polymorphonuclear leucocytes and plasma cells. The process appeared to extend into the adjoining hypothalamic structures and involved the tracts in the supra-optic, ventro-medial and posterior hypothalamic nuclei (Le Gros Clark) [7]. There was a proliferation of blood-vessels throughout these regions, more than is normally seen in this area.

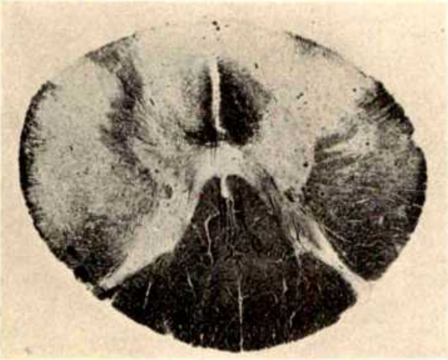

FIG. 3.—A. S. Section through the cervical segments of the spinal cord showing the diffuse nature of the demyelinization. Weigert-Pal's method.

Sections made at the level of the colliculi and the level of the caudal end of the mammillary bodies, showed the same type of affection of the tracts in both bases pedunculi. There was demyelination and destruction of axis-cylinders in a totally asymmetrical fashion of parts of the fronto-pontine, pyramidal, and temporo-pontine tracts.

On examination of the spinal cord the segments C4 and 5 were most severely involved. At this level there was a complete demyelination of the cord except for the dorsal half of the posterior column. From this region upward to C2 and downward to C8, the process was a continuous one, tending to diminish in severity as it approached these limits (fig. 3). In the lumbar segments there was similar but much less extensive disease. Wallerian degeneration was present in the spino-cerebellar and spino-thalamic tracts at C1 and in the pyramidal tracts in the dorsal and lumbar segments. Throughout most of the

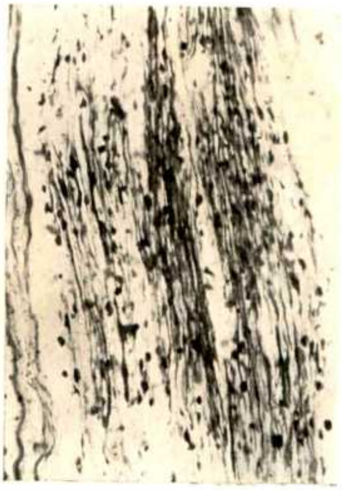

FIG. 2.

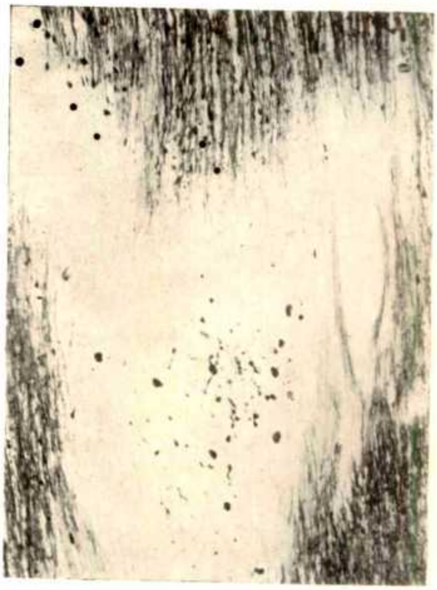

FIG. 4.

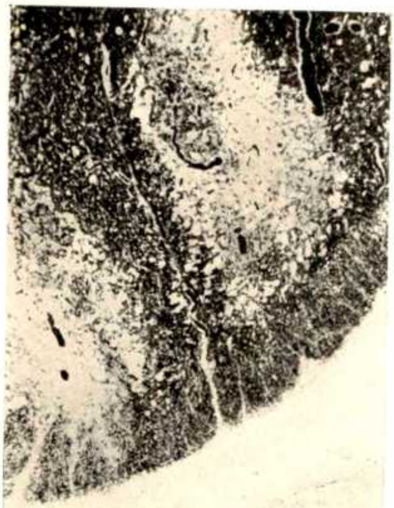

FIG. 5.

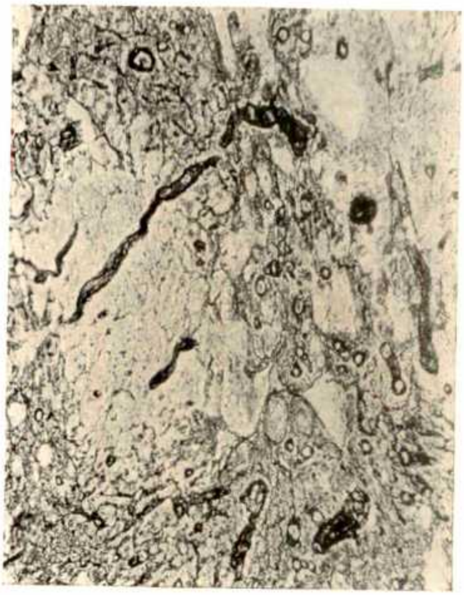

FIG. 6.

FIG. 2.—A. S. Section through optic nerves showing axis cylinders in a state of thickening, fragmentation or end-bulb formation, or completely destroyed. Gros-Bielschowsky counterstained with Van Gieson.

FIG. 4.—E. A. Section through the optic tracts showing early lesions in centre of right optic tract with perivascular destruction of axis cylinders. Gros-Bielschowsky's method counterstained with thionin blue.

FIG. 5.—E. A. Section through spinal cord at D9 showing cavity formation. Weil's method.

FIG. 6.—A. B. Section through spinal cord at C8 to show intense fibroplastic overgrowth. Perdrau's method.

To illustrate paper by Ben H. Balser.

demyelinated areas, there could be found many intact single sheaths. There was a perivascular infiltration of lymphocytes, plasma, and endothelial cells, throughout the cord and meninges, while in the cervical region polymorphonuclear cells were also present. In the more affected areas there was a proliferation of blood-vessels, but very little connective tissue. Thickening and end-bulb formation of the axis-cylinders was seen in the demyelinated areas of the cervical cord, but here again many of them were intact. There was very little glial fibre proliferation in any of the affected areas.

Case 2.—E. A., female, aged 50, was admitted to the National Hospital under Dr. E. A. Carmichael on March 9, 1935. She was perfectly well up to November, 1934, when she developed severe pain in the back associated with high fever and sweating. After three weeks in bed, she got up but had recurrence of the pain and temperature. A surgeon was called in at this time and he operated on her for a growth (?) of the right kidney which he removed. Improvement was slow thereafter, and five weeks later she was just able to get about by holding on to objects in the room. Three weeks later (four weeks prior to admission) she had a sharp, sudden pain in the right inguinal fossa, just above and parallel to Poupart's ligament. The pain would come every hour or so for a few seconds, and lasted about four days. Then, after a three-day interval there was a four-day period of intermittent hiccough, lasting thirty to sixty seconds at one to two-hour intervals. This also disappeared spontaneously. After another three-day interval, there followed a four-day period of retching, which occurred two or three times daily. There was no vomiting. Again followed a three-day interval of well-being. The patient then developed numbness in both feet, greater on the left than on the right, which slowly spread up the left leg to the buttock and groin, and up the left leg to the knee. Three days later (four days prior to admission), she was unable to stand alone because of weakness in both legs. At this time, numbness and weakness of the left hand and forearm appeared and spread rapidly up the arm. The following day she was unable to feel the passing of fæces or urine, but had a normal call to stool.

On examination in hospital the patient was a grey-haired, very thin, elderly woman, showing marked general wasting of subcutaneous fat of the limbs and trunk. Her mentality was unimpaired. The visual acuity, both right and left, was $\frac{6}{9}$, the fields were full to confrontation tests and the fundi appeared normal. There were no abnormalities of the other cranial nerves. The upper limbs were thin, but there was no localized muscular wasting and power was apparently normal in all muscle groups except the extensors of the left forearm. Tone was normal. There was no disturbance of co-ordination. She was unable to sit up without using her arms. Both lower extremities were thin with generalized subcutaneous wasting. Tone was slightly increased on both sides, and there was impairment of power in flexion and extension at the left ankle. Co-ordination was poor on both sides. All the tendon reflexes were increased and the abdominal reflexes were absent. There were bilateral extensor plantar responses. Complete loss to all forms of sensation was present up to the level of L1, with no sensory disturbance above this level. Examination of the other systems showed no abnormality except for the nephrectomy scar in the right loin. The spinal fluid protein was 110 mgm. per cent. and it contained 38 cells. The Wassermann reaction and colloidal gold curve was negative. The blood showed a leucocytosis of 12,200, of which 85·5 per cent. were polymorphonuclear cells.

Progress.—The patient rapidly became weaker. On March 17 the edges of both optic discs were blurred, but there was no gross visual defect. The weakness and sensory disturbance progressed so that examination on April 6 showed marked wasting of both upper limbs, more on the left than on the right, with moderate weakness of the left arm. Tone was diminished on both sides. There was a questionable sensory level to pin-prick at C2. Appreciation of vibration was present in both upper extremities, but position-sense was greatly diminished in the fingers of the left hand, though not of the right. Appreciation of size, shape, form and weight of objects, and two point discrimination were greatly disturbed in the left hand.

Her condition rapidly became worse, and she died on April 20.

Post-mortem examination.—The brain and cord were removed. There was a diffuse softening of the cord throughout the lower thoracic and lumbar enlargement, without much shrinkage. The lungs, liver, and spleen were normal. The heart was small and pale, with rather thin ventricular walls. The vessels of the heart were normal, but the mitral valve showed a marked thickening and dilatation of one cusp. The right kidney was absent, and the left showed slight inflammation in the pelvis. The bladder contained thick purulent urine.

As in the preceding case, pieces taken from the frontal and occipital lobes, the basal ganglia, through the optic chiasm and tracts with the neighbouring diencephalic structures, through the mesencephalon at its uppermost and lowest levels, and from the different segments and of the spinal cord were embedded in celloidin. These sections were stained by the Weil method for myelin sheaths, the Gros-Bielschowsky method for axis-cylinders counterstained with thionin-blue, the Mallory phosphotungstic acid hematoxylin method for neuroglia fibres and cells, and by the Van Gieson, Scharlach R and Perdrau methods.

The sections of the occipital and frontal cortex and the basal ganglia showed perivascular infiltration with lymphocytes and plasma cells. This was not very marked in degree or extent, but was definitely pathological. The occipital lobe and basal ganglia showed more involvement than the frontal lobe. Here the myelin sheaths tended to be crowded away by the dilated perivascular spaces, but there was no evidence of perivascular demyelination in these areas.

Serial sections were made through the optic tracts. In the centre of the right optic tract was a fairly large area of destruction of myelin sheaths and axis cylinders (Plate V, fig. 4), with a cellular infiltration of lymphocytes, plasma and endothelial cells. Polymorphonuclear cells were occasionally seen. Scattered throughout both optic tracts were smaller areas of perivascular demyelination and axis cylinder destruction which accompanied areas of perivascular infiltration containing the same type of cells as previously described. This infiltration was marked in the chiasm. Occasional intact myelin sheaths and axis cylinders were noticeable in each involved area. There was no glial fibre proliferation.

Sections through the upper and lower levels of the mesencephalon showed a more severe affection of the tracts of both bases pedunculi, but again in an asymmetrical fashion. There was demyelination, axis cylinder destruction, and beginning cavity formation. There was no glial or connective tissue reaction.

On examination of sections of the spinal cord, two areas of involvement with a relatively unaffected area between them were found. The upper and more severe affection was at C4 and C5, gradually diminishing in intensity toward C2 and C8. The lower was most severe at D6, diminishing in intensity up to D3 and down to L2. The area between, from C8 to D3, was intact except for Wallerian degeneration of the spino-cerebellar and spino-thalamic tracts. The region below L2 was also intact, except for Wallerian degeneration in the pyramidal tracts. A cavity formation was found at D9 (Plate V, fig. 5). The lower area was more severely involved than the upper, the cord being completely demyelinated at D6. Throughout the diseased areas occasional intact myelin sheaths and axis cylinders were seen. The axis cylinders were destroyed in the regions above described. Proliferation of blood-vessels was quite marked and was present even in what appeared to be unaffected areas. There was an intense perivascular infiltration of lymphocytes, plasma cells, and occasional polymorphonuclear cells, throughout the cord. There was very little proliferation of neuroglia fibres or connective tissue. Occasional giant astrocytes were seen in the proximity of engorged blood-vessels in the less affected areas.

Case 3.—A. B., female, aged 15, came under the care of Dr. C. P. Symonds on May 10, 1930. She was well up to January, 1929, when she contracted influenza which left her feeling generally weak. In July, 1929, while walking, she fell down and found her right leg numb and useless. The numbness rapidly disappeared, but the weakness in the right leg remained for three weeks and then cleared up. In September, 1929, she began to drag her left leg and again fell down a few days later. This time her left leg felt numb and useless. After three weeks in bed the right leg also became useless but both recovered by December. In January, 1930, she again dragged her right foot and fourteen days later her left foot. At this time the fingers of her left hand became weak and her vision became so badly affected that she was totally blind in her left eye in three or four days. Power in her legs and vision improved, but she could not fully extend the fingers of her left hand.

Examination.—On May 14, 1930, she had a visual acuity of $\frac{6}{18}$ on the right and $\frac{6}{24}$ on the left. There was a generalized constriction of both peripheral fields with a paracentral scotoma in the upper field of the left eye. There was pallor of the left disc. The left pupil failed to hold its contraction to light. The interoseii of the left hand were wasted, but there was no alteration in tone in the upper extremities. Power here was good and equal, except in the left hand where the grip was very weak and the fingers could not be extended or thumb adducted. There was a coarse tremor of the extended fingers. The muscles of the trunk and lower extremities were all wasted in a symmetrical fashion and tone was diminished. Power in the trunk and legs was greatly impaired, the left leg being more affected than the right, and more distally than proximally. The tendon reflexes were absent in the left upper and both lower limbs, but were very active in the right upper limb. The abdominal reflexes were absent. There was a complete loss of sensation to cotton-wool and pin-prick below D2 on the right and D4 on the left. Position sense and appreciation of vibration were intact in the upper extremities but absent in the lower. Her physical examination was otherwise normal. The cerebrospinal fluid contained 15 cells and 40 mgm. per cent. of protein. The Wassermann reaction and colloidal gold curve were negative.

She slowly and progressively became worse thereafter, and died in March, 1931.

Post-mortem examination.—Only the spinal cord was received for examination. It showed no gross abnormalities on naked eye inspection. Segmental sections were embedded in celloidin and stained by the Loyez, Aniline Blue-Orange G, Phosphotungstic Acid Hemotoxylin, Perdrau and Van Gieson methods.

A diffuse demyelinating process was present in the cervical and dorsal region. It was most severe from C8 to D4, decreasing in intensity down to D10 and going up as far as C4. In the region from C8 to D4, the entire cord was involved, yet occasional bundles of intact myelin sheaths could readily be seen. Below D10 both the pyramidal tracts showed Wallerian degeneration. In all of the affected areas there was a proliferation of smaller blood-vessels. The perivascular infiltration consisted of lymphocytes, plasma, and endothelial cells with occasional polymorphonuclear leucocytes. In the lumbar segments, the infiltration was greatest in the region of the anterior horns. There was very little glial tissue reaction. There was an intense fibroblastic overgrowth in the dorsal columns at C8 and D1, which gradually lessened in degree toward C6 and D4 (Plate V, fig. 6). Such a reaction was not seen in Cases 1 and 2. It was greatest around the blood-vessels and seemed to spread out from them.

Case 4.—M. K., a girl, aged 11 years, was admitted to the National Hospital under Dr. George Riddoch on March 13, 1935. She was well up to the beginning of 1933 when, during the first three months of that year, she developed consecutive attacks of acute nephritis, measles and whooping-cough. At the end of May, 1933, she returned home from school, complaining of general malaise, pain in the back, a cold and shivery feeling. She was restless that night, but the following day seemed to have recovered completely. After remaining in bed for three weeks she was allowed to be up, and one afternoon complained that her vision was blurred. This progressed rapidly so that two days later blindness was complete, apparently even to light perception. There were no other complaints. Blindness remained for about a week when the vision began to improve rapidly, so that by the early part of August it seemed to be quite normal (approximately five weeks after the onset of the blindness). Vision remained good for about six weeks, but in the early part of September there was a relapse. Vision again failed to such an extent that the patient could not see to read. The right eye was more affected than the left, and was, in fact, almost completely blind. She remained well, except for the visual defect, until the last week of February, 1935, when she came home from school one afternoon complaining of pain in both elbows and in the back, high up between the shoulder blades. After a week in bed these complaints cleared up, but on arising she was found to be more weak and unsteady than could be accounted for by the week in bed. She fell once or twice, from unsteadiness rather than weakness, and tended to stagger on walking.

Examination.—She was a thin but fairly well-developed girl, bright, alert and attentive. The right eye was blind even to light perception, but with the left eye counting fingers was possible at two feet. Both optic discs were clearly defined but paper-white in colour, the right more than the left. The physiological cups, vessels, maculæ and the retinæ showed no abnormalities. The visual field of the left eye showed a general constriction with a central scotoma. Convergence was poor, fixation being attempted with the left eye. The pupils were of normal size, equal and round, the right immobile to direct light but reacting consensually, the left reacting briskly to light and on convergence but failing to maintain the contraction. The lower extremities were both a little wasted. There was paresis of the flexors of the hip only. There was unsteadiness in heel-shin-finger tests but no gross ataxia. All the tendon-jerks were active, the knee and ankle jerks much more than the others. Only the right upper abdominal reflex could be elicited and the response was easily exhausted. There were bilateral extensor plantar responses, A sensory level to pin-prick and heat and cold, was present at D5-6, with a slight diminution in appreciation of cotton-wool stimuli as well. Appreciation of vibration was impaired in both lower extremities but position sense was intact. Her general physical examination was otherwise normal.

Progress.—She improved in hospital. The ataxia completely cleared up, the abdominal reflexes returned and the plantar responses became doubtfully flexor. The sensory level, although still definite, was nevertheless diminished. Her vision remained unchanged. She was discharged on March 29, 1935.

DISCUSSION.

Clinical diagnosis.—In differentiating neuromyelitis optica from acute disseminated sclerosis, it is known that the former disease may occur at any age, many cases being reported in children of 10 years, or even less. Disturbances of vision are dramatic, being bilateral and often progressing rapidly to complete blindness. The blindness may develop in the course of a few days with or without remissions and relapses. When remissions occur, careful examination usually shows permanent damage in the form of diminution of visual acuity, or scotomata. The visual disturbance may precede or follow the myelitic process. In those cases in which the spinal cord is involved before the optic pathways, the sensory disturbances are of primary importance. The occurrence of pain in the extremities and in the back, with a gradually ascending numbness in the extremities up to a distinct level, frequently in the lower cervical region, is a common mode of onset. This sometimes leads to an erroneous clinical diagnosis of spinal neoplasm. There is no mental disturbance, and involvement of the other cranial nerves, other than the optic, or of the cerebellum practically never occurs. Remissions in the disease as a whole, may or may not occur (Beck 10 per cent., Perritt 50 per cent.), and relapses are infrequent. Contrasted with this, disseminated sclerosis is a condition which occurs at puberty or later and which often involves vision in one eye but rarely in both eyes. Pain is an infrequent complaint but numbness is quite common. However, both these symptoms, when they present themselves, are usually localized and not progressive.

The post-infections and post-vaccinial acute disseminated encephalomyelitis can be differentiated more easily from neuromyelitis optica. This syndrome is frequently initiated by pain in the extremities and in the back and progressive numbness which usually does not stop at a level. The ataxia, disturbance of co-ordination and severe mental symptoms dominate the clinical picture. Differentiation is aided also by the history of preceding infection or vaccination, and the lack of involvement of the visual pathways in disseminated encephalo-myelitis.

Cerebrospinal fluid.—In neuromyelitis optica there may be an increase in polymorphonuclear cells in the cerebrospinal fluid. The colloidal gold curve is negative. In this disease there may be also a relative or absolute increase in polymorphonuclear cells in the blood. In disseminated sclerosis, if pleocytosis of the cerebrospinal fluid is present, there are few, if any, polymorphonuclear cells, and changes in the celloidal gold curve, of the paretic type, occur in about 25 per cent. of cases (H. H. Merritt). In both diseases the spinal fluid protein may or may not be increased and this determination is of no value in differentiation.

Pathological diagnosis.—Neuromyelitis optica, as summarized from the cases herein reported, is characterized by an asymmetrical diffuse demyelination of the cord, brain-stem, and optic nerves and tracts.

From the study of early lesions of the optic tracts (serial sections in Case 2), it appears that the lesions are perivascular and may be in the centre of the tracts at first, and extend or coalesce so that there soon appears a central core of destruction of myelin sheaths and axis cylinders. This, in many instances, may not occur. The process in the spinal cord tends to be continuous in nature, rather than spotty, and islands of intact myelin sheaths or isolated sheaths are present in affected areas, in which regions cavity formation also may be found. The axis cylinders show thickening, fragmentation, and end-bulb formation, although many of them may be entirely intact. There is a considerable proliferation of blood-vessels and a perivascular infiltration consisting predominantly of lymphocytes and plasma cells. Polymorphonuclear leucocytes can also be demonstrated in some of the involved areas. Only occasionally increase in glial cells is seen. This perivascular infiltration may be found to be present throughout the central nervous system to a greater or lesser degree. Occasional giant astrocytes are seen in the proximity of an engorged blood-vessel or capillary. There is only a slight, if any, proliferation of neuroglial fibres and connective tissue, at least in the early acute non-remissive stage. However, a dense fibrous tissue overgrowth may occur later in the disease and may be seen extending from the infiltrated blood-vessels (Case 3).

Contrasted with this pathological picture, in acute disseminated sclerosis the demyelinated areas are usually "punched out" in appearance rather than infiltrating at their borders, with complete destruction of all myelin sheaths within the involved areas, whereas there are always small bundles of intact myelin sheaths in neuromyelitis optica. The axis cylinders are usually intact. The involved areas may be asymmetrical, but are not continuous as in neuromyelitis optica, and cavity formation does not occur. Polymorphonuclear cells are not seen, the perivascular infiltration which is present being composed chiefly of lymphocytes and plasma cells with some compound granular corpuscles. There is an abundance of neuroglial fibres and cells. Any part of the central nervous system may be affected.

Pathologically, acute disseminated encephalomyelitis is an asymmetrical diffuse demyelinating disease which is distinctly perivascular in nature. Throughout the white matter of the brain and brain-stem, the sub-ependymal zones, and the marginal zones of the spinal cord may be seen small discrete areas of myelin sheath and axis cylinder destruction, varying in size, but not coalescing as in neuromyelitis optica. Simultaneously, with or without demyelination, there is a perivascular gliosis consisting of microglia and a perivascular infiltration consisting of lymphocytes and plasma cells, but polymorphonuclear leucocytes are not present.

The pathological process in diffuse sclerosis resembles that of neuromyelitis optica. The optic nerves and tracts may show changes, the early lesions in them being similar to those in neuromyelitis optica. That is, there is a perivascular myelin sheath and axis cylinder destruction lying centrally in the tracts, and tending to produce a central core of destruction (Alfred Meyer). The demyelination of the centrum ovale is diffuse in nature, the axis cylinders being involved, sometimes to complete destruction. Early in the disease the perivascular infiltration may be slight, but soon increases in severity and is composed of lymphocytes, plasma and gitter cells. Large globoid and multinucleated giant cells found at the periphery of the lesions have been described (Stewart, Greenfield and Blandy [4]), but these are not seen in neuromyelitis optica. With progression of the disease there is a moderate proliferation of connective tissue and neuroglial fibres in the affected areas. Large giant astrocytes are occasionally seen. Wallerian degeneration is usually present.

In the Withering lectures of 1935, Weston Hurst [6] has pointed out that the perivascular infiltration found in the central nervous system in virus diseases is a reactive phenomenon; that the neurotropic viruses are essentially cytotropic in their affinity; and that there is no known virus disease of human beings in which the virus will produce demyelination on injection into susceptible animals. On the other hand, the perivascular nature of the myelin sheath and axis cylinder destruction, with an increase in polymorphonuclear cells in both blood and spinal fluid, and their presence in the perineural and perivascular spaces, would speak for a toxic or infectious process in the blood stream which has, apparently, an affinity for the central nervous system. For the present, therefore, it does not seem likely that neuromyelitis optica is due to a virus. The field of study of virus diseases and their pathogenicity is relatively new, and with more study of the demyelinating diseases, it is possible that a virus may be isolated and proved to be the ætiological factor in neuromyelitis optica.

Beck had indicated that 35 per cent. of the cases he reviewed consisted of disseminated foci, while in the remaining 65 per cent. there was a diffuse myelitis varying in extent from three segments to an involvement of all of the thoracic and many of both the lumbar and cervical segments. He considered that "it is possible that these two types represent two distinct diseases with a common clinical picture." Cases 1 and 2 herein reported are "disseminated" in the sense that there are at least three separate areas of involvement. In Case 1 most of the cervical and some of the lumbar segments are involved, with complete sparing of the dorsal segments. The brain stem is also involved. In Case 2 the segments from C2 to C8 were affected with a clear area, except for Wallerian degeneration, from C8 to D3, and the remaining dorsal segments are severely affected. Here again the brain stem was involved. Case 3 represents the "diffuse" type, since there is one continuous involvement from C4 to D10. Except for this difference in distribution of the lesions, the pathology is exactly the same in all three cases. Since the clinical picture is the same in all cases, it does not seem justifiable to assume a difference in diseases on the basis of distribution alone, unless by the term "disseminated," Beck had intended many small foci in the cord with some differences in the clinical and pathological studies.

Remissions in a disease with such severe pathology are surprising. It might be assumed, however, that the very rapid clinical changes are due, in a large measure, to an extensive reactive process which interferes with physiological function. Although reports are made of complete recovery of function in both optic nerve and cord, there may well be some permanent damage which remains so small as not to be readily detected.

(The author wishes to express his appreciation and thanks to Dr. J. Godwin Greenfield for his constructive criticism of this work, and to Drs. Gordon Holmes, E. Arnold Carmichael, C. P. Symonds and George Riddoch for permission to use the cases herein reported.)

BIBLIOGRAPHY.

[1] Allbutt, T. C. "On the Ophthalmoscopic Signs of Spinal Disease. *Lancet*, 1870, **1**, 203.
[2] Devic, C. *Thèse de Lyon*, 1894. Congrès français de medicin, 1894, i, 139.
[3] Beck, G. M. "Diffuse Myelitis with Optic Neuritis," *Brain*, 1927, **50**, 687.
[4] Stewart, T. G., Greenfield, J. G., and Blandy, M. A. "Encephalitis Periaxialis Diffusa," *Ibid.*, 1927, **50**, 1.
[5] Symonds, C. P. "The Pathological Anatomy of Disseminated Sclerosis," *Ibid.*, 1924, **47**, 36.
[6] Hurst, E. Weston. "The Neurotropic Virus Diseases," *Lancet*, 1935, ii, 697.
[7] Le Gros Clark, W. E. "The Topography and Homologies of the Hypothalamic Nuclei in Man," *Journ. Anat.*, 1936, **70**, 203.

THE SIGNIFICANCE OF INDIVIDUAL DIFFERENCES IN THE BERGER RHYTHM.

BY FREDERICK LEMERE.

MANY investigators [1, 2, 3, 4, 5] working on the electrical potentials of the human cortex have noticed that individuals differ in the facility with which these potentials may be obtained. Some subjects could be counted on to produce good rhythmic waves under favourable circumstances, while others never seemed to be able to give a satisfactory rhythm under any condition. The ability or inability to produce a strong Berger rhythm, therefore, seems to be an individual characteristic which it will be the purpose of this paper to investigate more thoroughly. To begin with, the Berger rhythm was studied in twenty-six normal subjects. In order to determine the degree of variation of the rhythm in any one given individual, from three to five electro-encephalograms were obtained from each subject within a period of a month or less.

The electrical potentials emanating from the brain were picked up by moist pad electrodes which were 2 cm. in diameter and were soaked in saline solution before being applied to the scalp. One electrode was usually placed on the forehead and the other on the occiput.

The amplifying unit consisted of a five stage condenser-coupled amplifier with a balanced (push-pull) input stage as described by Matthews [6]. This latter feature was very useful in balancing out extraneous electrical disturbances. The recording unit was a Matthews' ink-writing oscillograph. For the purposes of comparison, the amplification was kept constant within narrow limits.

The subjects were examined lying down in a quiet room with instructions to relax as much as possible both mentally and physically. Although Berger [7] has emphasized the importance of complete exclusion of outside stimuli in his criticisms of other worker's results, control experiments did not seem to bear this out. Some of the patients in this series were tested on a busy, noisy, open ward and subsequently in a quiet darkened room with no difference in the rhythms produced.

THE BERGER RHYTHM IN NORMAL SUBJECTS.

The most obvious rhythm was that of the alpha (10 per second) waves of Berger. As Adrian [1 and 8] and his co-workers have shown, these waves arise, for the most part, from the visual cortex, and were usually present only with the eyes shut. Alpha waves with the eyes open were observed in only two subjects, and then to a much less degree than with the eyes shut[1]. It is recognized that a 10 per second rhythm may arise in other parts of the brain than the visual cortex [9], but such extraneous "alpha" waves have little bearing on the present investigation. With the leads and method used, these waves are insignificant when compared with those coming from the visual cortex with the eyes closed.

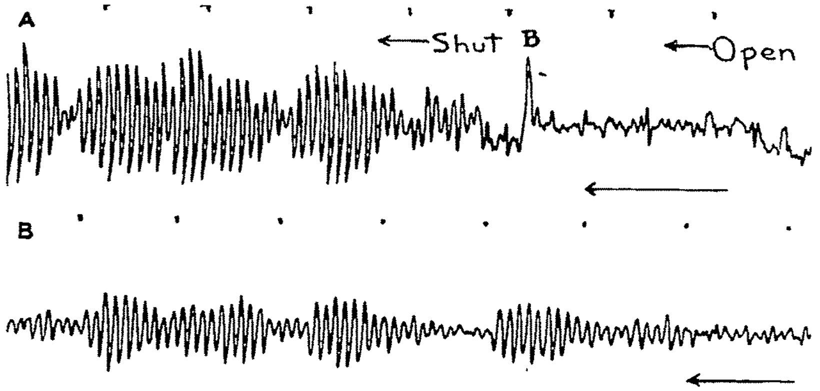

FIG. 1.—Representative sections of records from a subject with a "good" Berger rhythm. Time in seconds. A, normal record with subject relaxed mentally and physically, eyes shut at B. B, record obtained during the same trial as A but with eyes shut and carrying on a light conversation. The alpha (10 per second) waves begin as soon as the eyes are closed.

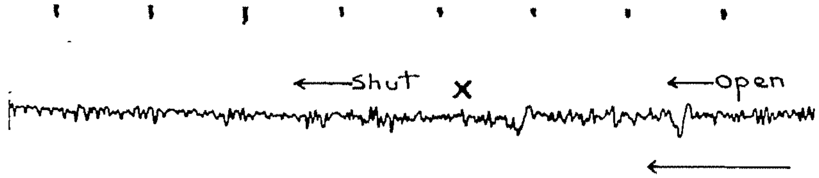

FIG. 2.—Representative section of a record obtained from a subject showing almost no alpha (10 per second) waves, but "good" beta (20 per second) waves. Eyes shut at X. Time in seconds.

For the purpose of comparison, the alpha rhythm was classified on the basis of its amplitude, regularity, and constancy. A record was considered to show a "good" rhythm when the alpha waves were of above average amplitude (usually over 0·05 millivolts), constancy, and regularity (fig. 1). A "poor" rhythm (fig. 2) was expressed by irregular and inconstant alpha waves of low amplitude (usually less than 0·05 millivolts). The amplitude of the alpha waves was judged not only by their height but also in relation to the amplitude of the irregularities of the base line. These irregularities were partly due to the primary "noise" of the apparatus (fig. 3) and partly to the complex potentials

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[1] These two subjects, producing occasional groups of alpha waves with eyes open, showed strong constant 10 per second waves with eyes open or shut when a bifrontal lead was used.

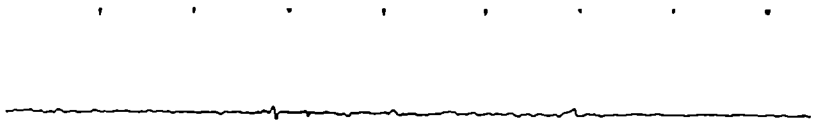

FIG. 3.—Base line produced by apparatus alone with 5,000 ohms resistance across the electrodes.

from the brain, other than those causing the alpha waves. As such, the base line with the eyes open served as a measure both of the sensitivity of the apparatus and also of the general electrical activity of the brain as opposed to that of the occipital cortex.

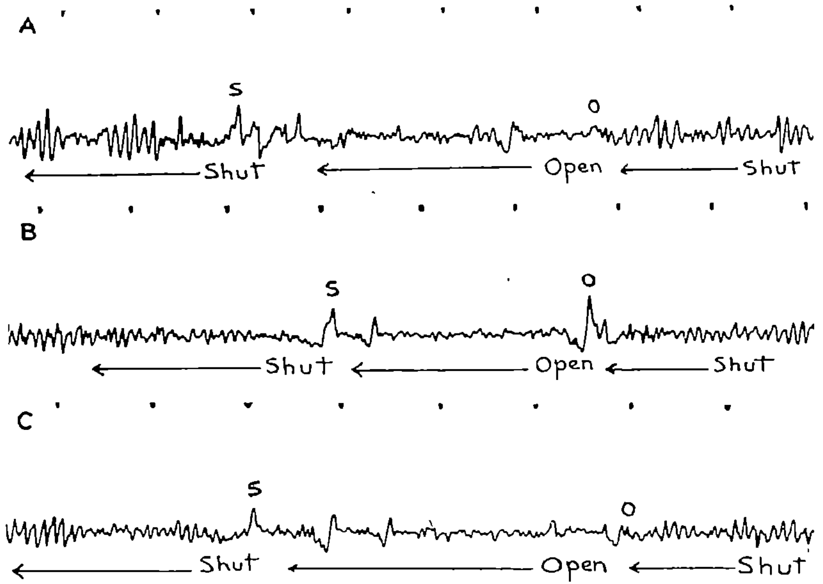

FIG. 4.—Representative sections of records from the same subject at different times. Time in seconds. Eyes opened at O and shut at S. A, first trial. B, third trial, waves not quite as "good" as in A although subject more relaxed. Shows the usual tendency for the waves to get slightly "worse" on subsequent trials. C, fourth trial, one week after B and during examinations. "Keyed up" but not worried. Less relaxed than in B.

The number of subjects showing "good" waves was about equal to that showing "poor" waves. In any one subject, there was a remarkable similarity between the records taken at different times. Only four gave "good" waves at one time and "poor" waves at another time. Of these, two gave "poor" waves in relation to a state of acute anxiety (a secret engagement and an important Rugby match).

There was a definite tendency for the alpha waves to become slightly "poorer" on subsequent trials (fig. 4, A and B). The time of the day when examined, the spacing of the trials, the mood, or the degree of tiredness could not be correlated with any changes in the waves.

The rate of the rhythm was also remarkably constant even in different subjects. In this series, the rhythm of the alpha waves was never faster than 12 per second or slower than 9 per second. Only five showed a change in rate at different trials and this did not vary more than one beat a second from the usual rate for that subject. There was no correlation between the size of the alpha waves and their rate.

As others have observed, difficult mental effort or disturbing external stimuli have a tendency to lower the alpha waves. On the other hand, in this series, an individual showing "good" waves continued to do so even when disturbed by being asked to carry on a conversation (fig. 1, B).

Berger's beta waves, those with a rhythm of from 20-40 per second, are less well understood. They were present with the eyes open or shut and seemed to be the strongest in those subjects having "poor" alpha waves (fig. 2).

THE SIGNIFICANCE OF INDIVIDUAL DIFFERENCES IN BERGER RHYTHM.

The first question that arises is whether a quantitative comparison of the rhythms in different individuals is valid. May not physical factors, such as the thickness of the skull or the resistance of the scalp, determine whether an individual has "good" or "poor" waves? The main objection to a physical explanation of individual differences is the variability of the waves even in the same record. The variation in the regularity and size of the waves produced by drugs [2], psychological factors, and the tendency for the alpha waves to decline on subsequent trials are all more easily explained on a physiological than on a physical basis. One would expect the physical factors to remain rather constant.

The resistance between the electrodes was measured in a number of subjects during the recording of the Berger rhythm and no correlation found between "good" or "poor" waves and the inter-electrode resistance. The resistance through the dura and skull was also measured in several cadavers and found to be between 900 and 1,100 ohms, a variation inadequate to explain the differences in rhythm that would undoubtedly have been observed during life.

An even more significant bit of evidence against a physical explanation of the individual differences in Berger rhythm is that obtained from patients with unilateral diagnostic trephine openings in the occipito-parietal region. Three such patients, who subsequently were found to have no cerebral lesions, were available. Leads from the trephined side showed waves of somewhat greater amplitude, but no greater regularity or constancy than those from the normal side (fig. 5). Even then, the differences were much less than those between persons showing "good" and "poor" waves.

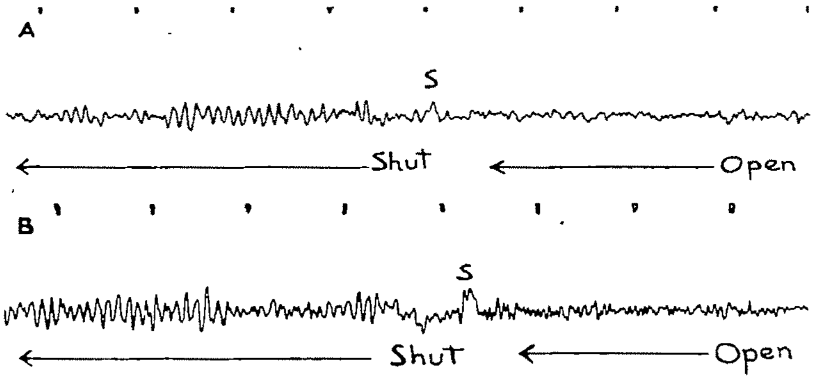

FIG. 5. Representative sections of records from a patient with a diagnostic right-sided occipito-parietal trephine. Subsequently proven not to have any cerebral lesion. A, record from left (normal) side of the head. B, record from right (trephined) side of the head. Occipital electrode over trephine. Time in seconds. Eyes shut at S.

Could not these individual differences be explained by differences in the ability to relax? Again the results did not bear this out. Several reliable subjects stated that they were most tense and had the greatest difficulty in keeping from thinking during the trial that showed the "best" alpha waves. There was also a general tendency for the waves to get "worse" with subsequent trials although relaxation became better. Ten of the subjects had examinations during the week of their last trial. There was no change in seven, but three showed "better" waves during this week (fig. 4, C). Significantly, these three stated that although they were "keyed up" they were not worried about the examinations. This suggests that a general feeling of tension may make the waves "better," but that worry or anxiety may neutralize this effect.

Another mental characteristic that one might expect in people showing "good" waves would be the ability to concentrate, so to speak, on thinking of nothing. Those showing "good" waves did seem to have good powers of concentration in general, but often stated that thoughts were flying through their mind even when the record showed a strong Berger rhythm. On the other hand, subjects with "poor" waves were able to completely banish all conscious activity with no improvement in the Berger rhythm.

The most interesting question of all is whether there are any obvious personality differences between those having "good" and those having "poor" waves. The physical make-up, sex, intelligence, memory capacity, introversion or extroversion, and auditory or visual memory, suggested themselves as possible differentiating points but no correlation could be found between these and the ability or inability to produce alpha waves. Although no special psychological or personality tests were given to these subjects, most of them were questioned from a psychiatric point of view. My impression was that "good" waves were produced in general by the cyclothymic or manic-depressive type of individual while schizoid personalities gave "poor" waves as a rule. It was, therefore, decided to test this theory out in psychotic patients.

THE BERGER RHYTHM IN PSYCHOTIC PATIENTS.

Electro-encephalograms were obtained from forty psychotic patients using the same procedure as for the normal subjects. Only patients who could co-operate and in whom the diagnosis was fairly clear were examined. It was soon found that senile, arteriosclerotic, or deteriorated patients had to be excluded from the group used for analysis as such processes usually seemed to preclude the production of a "good" alpha rhythm. In other words, the manic-depressive changes occurring in involutional or pre-senile cases could not properly be used in this investigation in judging as to whether a patient had a schizoid or a cyclothymic make-up. However, when young patients in a mild or recovered stage of their illness were examined, a marked difference was found in the waves produced by the two groups. Consistently "good" waves were given only by the manic-depressive patients. Schizophrenic patients, on the other hand, rarely gave "good" waves (fig. 6) and then never consistently and only when they seemed to be stimulated by such

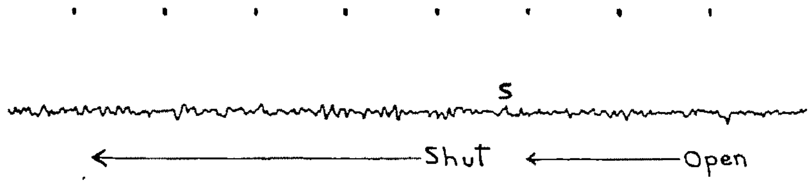

FIG. 6.—Representative section of a record taken in a patient with simple schizophrenia. Apparently normal at time the record was taken but gave history of attacks of marked apathy with feelings of unreality and reference.

things as visits from relatives or changes in their ward routine. It seemed that the apathy and affective deficiency of the schizophrenic was the feature of the illness most clearly related to an absent or " poor " alpha rhythm. The difference in the two groups could not be accounted for by different abilities to relax as the hypomanic patients (fig. 7) gave just as good waves as the depressed patients (fig. 8) who were completely relaxed. Nor was the difference one of mental activity for, as nearly as could be told, the manic patients were full of ideas while the depressed and simple schizophrenic patients seemed to be able to keep from thinking too much during the tests. Fortunately, at this time I had access to a group of disseminated sclerosis patients who were being examined in detail as to their emotional and intellectual capacities. This was being done in relation to the emotional instability that is frequently a symptom of this illness [1].

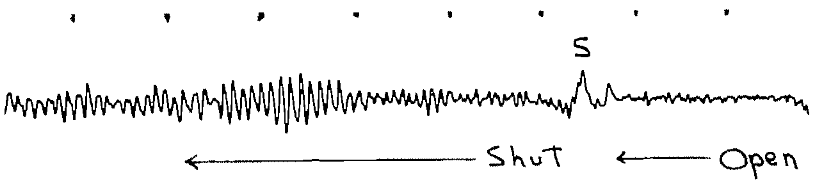

FIG. 7.—Representative section of a record taken in a patient in the hypomanic stage of a manic-depressive illness.

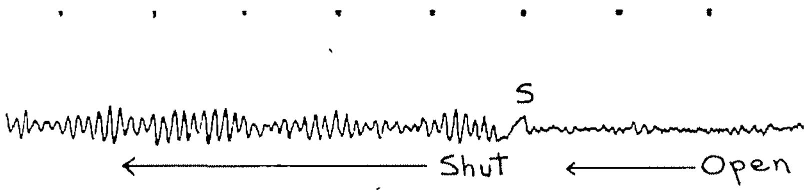

FIG. 8. Representative section of a record taken in a patient in the depressed phase of a manic-depressive illness.

THE BERGER RHYTHM IN DISSEMINATED SCLEROSIS.

Electro-encephalograms were taken by the usual procedure in eighteen cases of disseminated sclerosis. The records from five of these patients had to be disregarded as again there were signs of mental deterioration that invalidated the findings. Of the remaining thirteen patients, six complained of emotional instability as an early and troublesome symptom. Five of these six patients had "good" Berger rhythms (fig. 9) in contrast to the remainder of the group who had average or "poor" rhythms (fig. 10).

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[1] I wish to thank Drs. Frank Braceland and Jack Griffin who were doing this work, and who were kind enough to allow me to go over their notes on these patients.

According to current psychiatric concepts, emotional lability is probably due to the uncontrolled expression of an underlying cyclothymic personality. If this is true, then a "good" rhythm is again associated with an innate capacity for affective expression. At any rate, excluding the cases showing mental deterioration, there was a definite and close relationship between a "good" Berger rhythm and the symptom of emotional lability.

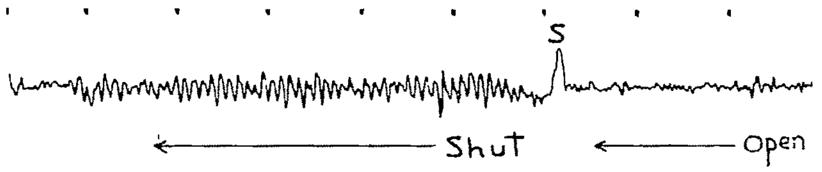

FIG. 9.—Representative section of a record obtained from a patient with disseminated sclerosis and who complained of emotional lability as an early and pronounced symptom. Shows a "good" Berger rhythm.

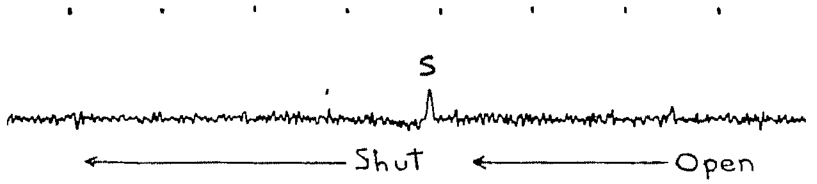

FIG. 10.—Representative section of record from a patient with disseminated sclerosis in whom there was no emotional lability. There is almost no Berger rhythm.

SUMMARY AND CONCLUSIONS.

From three to five separate electro-encephalograms were obtained at varying intervals from twenty-six normal adults. The object was to compare the Berger rhythm in different individuals and also in the same individual at different times.

The cerebral potentials were picked up from the scalp by moist pad electrodes. A balanced input amplifier was used in conjunction with an ink-writing oscillograph. Subjects were examined lying down, in a quiet room, and in as relaxed a state as possible.

The most obvious rhythm was that produced by the alpha waves (the 10 per second potentials from the visual cortex when the eyes are shut). Some subjects produced "good" alpha waves of relatively high regularity and amplitude (usually over 0·05 millivolts). In others, the waves were "poor," being irregularly present and of low amplitude (usually under 0·05 millivolts).

In any one subject, the ability or inability to produce "good" alpha waves remained remarkably constant. There was a slight tendency, however, for the waves to become "worse" on subsequent trials. Moderate disturbances, such as the noise of an open ward, had little effect on the waves as long as the subject lay quietly with his eyes closed.

The rate of the alpha waves varied between 9 and 12 per second in different subjects but never more than one beat per second in the same subject. There was no correlation between the rate and quality of the alpha waves.

Faster, beta rhythms (18 to 35 per second) of low amplitude were observed with the eyes open or shut. In general, they were the most obvious in those individuals with "poor" alpha waves.

Neither the time of day when examined, the spacing of the trials, the mood, the degree of tiredness, the physical type of the subject, the sex, the intelligence, nor the type of memory, auditory or visual, seemed to matter in the production of the alpha waves. Physical factors, such as the thickness of the skull, probably have little to do with individual differences in the Berger rhythms. As long as the subject co-operated in trying to relax, his ability or inability to do so seemed to have little effect on the quality of the waves produced.

The ability to produce "good" alpha waves seems to be a neurophysiological characteristic which is related in some way to the affective capacity of the individual.

Mildly manic or depressed patients give a "good" Berger rhythm provided that there are no associated presenile or arteriosclerotic changes or signs of mental deterioration. Schizophrenic patients nearly always give a "poor" rhythm. Normal individuals with cyclothymic or schizoid personalities show the same differences.

The close relationship of "good" waves to affective capacity is further suggested by the findings in patients with disseminated sclerosis. In these patients, those exhibiting emotional instability as an early symptom usually showed much better waves than those not troubled with this symptom.

This work was financed by a Rockefeller Foundation Grant and was carried out in the Physiological Laboratories, Cambridge; the Cambridgeshire Mental Hospital; the National Hospital, Queen Square, London; and the Colney Hatch Mental Hospital, London. I wish to express my very great indebtedness and appreciation to the staffs of the above institutions, and especially to Professor Adrian of Cambridge, for their kindness in providing the facilities for this investigation.

REFERENCES.

[1] ADRIAN, E. D., and MATTHEWS, B. H. C. "The Berger Rhythm: Potential Changes from the Occipital Lobes in Man," *Brain*, December, 1934, **57**, 355.

[2] BERGER, HANS. "Das Elektrenkephalogramm des Menschen," *Die Naturwissenschaften*, 1935, **23**, 121.

[3] GIBBS, F. A., DAVIS, H., and LENNOX, W. G. "The Electro-encephalogram in Epilepsy and in Conditions of Impaired Consciousness," *Arch. Neurol. and Psychiat.*, December, 1935, **34**, 1133.

[4] JASPER, H. H., and ANDREWS, H. L. "Human Brain Rhythms. I. Recording Techniques and Preliminary Results," *Journ. Gen. Psychol.*, 1936, **14**, 98.

[5] TÖNNIES, J. F. "Die unipolare Ableitung elektrischer Spannungen vom menschlichen Gehirn," *Die Naturwissenschaften*, February, 1934, **22**, 411.

[6] MATTHEWS, B. H. C. "A Special Purpose Amplifier," *Journ. Physiol.*, March 17, 1934, **81**, 28 P.

[7] BERGER, HANS. "Ueber das Elektrenkephalogramm des Menschen," *Arch. f. Psychiat.*, June, 1935, **103**, 444.

[8] ADRIAN, E. D., and YAMAGIWA, K. "The Origin of the Berger Rhythm," *Brain*, September, 1935, **58**, 323.

[9] FOERSTER, O., and ALTENBURGER, H. "Elektrobiologische Vorgänge ander menschlichen Hirnrinde," *Deutsch. Zeit. f. Nervenheilk.*, 1935, **135**, 277.

A NOTE ON THE PATHOLOGY OF SENILE CHOREA (NON-HEREDITARY).

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(*From the National Hospital, London.*)

SENILE chorea has been recognized as an entity by many writers (Collier and Adie [1], Brain [2], Critchley [3]), and may be defined as a condition coming on gradually in late middle life and characterized by generalized choreic movements. It is unaccompanied by mental change, and its onset is usually later in life than that of Huntington's chorea.

These facts would, clinically at any rate, seem to divide it as an entity from Huntington's chorea.

These cases are sometimes, rather unfortunately, known as chronic progressive chorea, although this term is more usually applied to Huntington's chorea. For example Davison [4], who records three cases under this title, takes as his first case one in which there was a clear family history of chorea, the second a doubtful family history of chorea but a plain one of mental changes, and although in his third case there was no family history, yet there was considerable mental change. These, therefore, can only be regarded as cases of Huntington's chorea.

Critchley [3] mentions the condition in his " Neurology of Old Age " and lays down the criteria mentioned above. He states that when these are applied rigidly it is a rarity. He states that the physical signs differ only slightly from those of Sydenham's chorea, except that the movements are perhaps of a wider amplitude, and that a pendular or a sustained knee-jerk is not seen in senile chorea.

He only touches briefly on the pathology of the condition, quoting Jakob [5], who says that senile chorea has been associated with a degeneration of the pallidal, but more particularly of the striatal cells, together with changes in the corpus dentatum. Jakob does not, however, describe clinical cases of senile chorea.

Although it has been recognized by these writers, there is no record of clinical cases with histological studies.

An opportunity presented itself of studying the brains of two patients who, during life, presented only chorea without either mental symptoms or a family history, and who therefore could not be classified as suffering from Huntington's chorea. It is hoped that this study may be of some assistance in elucidating the problem of chorea, especially as this type of case does not seem to have been extensively studied hitherto.

Methods.—It is always difficult to gauge the size of any particular part of the brain in relation to the size of the whole brain. In order, therefore, to estimate the amount of shrinkage of the constituent ganglia of the corpora striata, both in relation to each other and to the normal, the following method was suggested:—

Serial sections of the basal ganglia were cut, stained by Mallory's phosphotungstic acid hæmatoxylin method and their different parts were outlined under a camera lucida with constant magnification (× 4½). The area of the different structures in these drawings was then measured by a planimeter. These measurements were then compared with similar sections of three normal brains, which were cut, stained and drawn in the same way. By this simple method it was easy to estimate the size of any nucleus in section, but various facts made it impossible to measure the depth of the nuclei, and therefore the examination was limited to a comparison of their horizontal area.

Intermediate sections were stained by the Nissl, Loyez, Weigert-Pal and hæmatoxylin and van Gieson methods, and sections of the cortex of the frontal, pre- and post-central, and occipital areas, the cornu ammonis, and the pons and mid-brain were cut and stained by the same methods.

Material.—3 normal brains, 2 cases of senile chorea, and 3 cases of Huntington's chorea were examined in this way. In one of the cases of senile chorea a whole brain was available, but in the other only parts could be investigated as it had already been cut for routine examination.

Case 1.—A. F., aged 62, was admitted to the National Hospital under the care of Dr. F. M. R. Walshe in 1926.

Family history.—His father died of tuberculosis. His mother of old age at 75. There was no family history of chorea or insanity.

Past history.—He had an accident in 1924 without loss of consciousness.

History of his present complaint.—During the year before admission to hospital there had been choreic movements which had been generalized from the start. These had increased gradually, but there had been very little progression for three months before admission. Loss of weight had taken place during this year. He was not conscious of any mental deterioration and stated that his memory was quite good. His sleep had been fitful. The sphincters, ears and eyes, were normal.

On examination at the time of admission, he was an old, poorly nourished man, who went through a series of grotesque choreiform movements. These varied in intensity and were increased under mental or physical effort. They were not the fine movements of a Sydenham's chorea; instead of individual finger movements there was a simultaneous flexion of all the fingers *en bloc*. Movements were most marked in the abdomen, hands and feet. The face seemed relatively less active. There were frequent snarling movements of the lips. The abdominal muscles showed a constant procession of writhing movements. Under strain there was a wild purposeless flail-like slapping about of the forearms.

Speech was extremely difficult to understand as his tongue rolled about in his mouth continually.

Co-ordination tests were well performed, when the chorea was allowed for. There was no rigidity nor spasticity, the tendon-jerks were present and equal, and the plantars were flexor.

He was examined by the psychiatrist attending the hospital, Dr. Bernard Hart, who found that his mental condition was normal.

He remained in very much the same condition and was transferred to another hospital, where he died three years later.

Case 2.—A. B., aged 56, was admitted to St. Charles Hospital, where he died on November 10, 1933.

The notes available from this hospital are unfortunately not so full as in Case 1. There was no family history of chorea or insanity.

He had had choreiform movements of the lips, hands, arms and legs for eight years, which had gradually increased in severity. In addition to this he had some disorder of articulation. There had been no memory loss or mental change.

He was seen there by Dr. J. P. Martin who confirmed the fact that there was no mental change, and on examination noted the generalized chorea, and found that his tendon-jerks were present and equal and that his plantars were flexor; apart from the chorea no abnormal physical signs were detected in the examination of his nervous system.

The Wassermann reaction on the blood was negative.

Measurements.—Portions of the brain of Case 1 had already been embedded in celloidin and mounted on blocks, while the brain in Case 2 had been cut through the basal ganglia by the usual transverse section, and therefore the basal ganglia had to be mounted in two pieces, and it was not possible to estimate the loss of material between the two pieces. It was therefore possible to measure only the horizontal area and to compare the figures obtained with similar measurements of normal brains and of the brains from subjects of Huntington's chorea.

An effort was made to determine accurately the levels of the various sections in the different cases.

Caudate nucleus.—There was little difficulty in comparing the size of this ganglia in different brains as its area only changes from 0·184 to 0·164 square inches, or 0·172 to 0·15 over a depth of 5 mm. in the normal; therefore a very fair comparison can be made.

Comparative readings in square inches of the actual stained structure :—

	Sq. inches		
Three normal brains ..	0·165	0·142	0·175 = Average 0·161
Senile chorea	Case 1	0·073	
Senile chorea	Case 2	0·129	
Huntington's chorea ..	Case 1	0·053	
Huntington's chorea ..	Case 2	0·065	

Putamen.—As this structure lies lower than the caudate, the upper limit came within the blocks embedded, so that with a series of sections right through the blocks it was possible to get sections which were the same distance from the top of the putamen.

At lower levels the relative positions of recognizable tracts, as Vicq d'Azyr's bundle, the anterior commissure, &c., were used to determine the levels, and it was found by comparison in the normal cases that levels so determined were nearly correct in all cases.

The readings at three corresponding levels were :—

	Sq. inches		
Level I—			
Three normal brains ..	0·182	0·202	0·193 = Average 0·192
Senile chorea	Case 1	0·114	
Huntington's chorea ..	Case 1	0·048	
Huntington's chorea ..	Case 2 R.	0·071	
	L.	0·068	
Level II—			
Three normal brains ..	0·376	0·333	0·323 = Average 0·344
Senile chorea	Case 1	0·182	
Senile chorea	Case 2	0·296	
Huntington's chorea ..	Case 1	0·113	
(Huntington's chorea ..	Case 3	0·226)[1]	
Level III—			
Three normal brains ..	0·359	0·336	0·321 = Average 0·339
Senile chorea	Case 1	0·131	
Senile chorea	Case 2	0·301	
Huntington's chorea ..	Case 1	0·124	
(Huntington's chorea ..	Case 3	0·221)[1]	

[1] Weigert-Pal's method of staining which gives less shrinkage of the material was used. These figures are therefore not really comparable.

The globus pallidus.—This ganglion is spherical in shape and hence slight differences in level make more difference in size of the area than it does in the caudate or putamen. The figures therefore are only approximate. It was, however, possible to obtain a series of sections through the globus pallidus and the measurements of its area as seen in sections in the different cases were taken at the same distance from the upper margin of the ganglion, where the level was confirmed by the position of the recognizable tracts.

		Sq. inches	
Three normal brains ..	0·161	0·149	0 156 = Average 0·155
Senile chorea	Case 1	0·121	
Senile chorea	Case 2	0·107	
Huntington's chorea ...	Case 1	0·079	

Thalamus.—Here the level was fairly easy to determine both by the internal arrangement of its divisions and by its external relations. It also remains the same size through a series of several sections, but varies more than the other structures from one normal to another. The measurements at three different levels are given.

		Sq. inches		
Level I—				
Two normal brains ..		0·211		0·190 = Average 0·201
Huntington's chorea ..	Case 1		0·203	
Huntington's chorea ..	Case 2		0 233	
Level II—				
Two normal brains ..		0·529		0·489 = Average 0·509
Senile chorea	Case 1		0·544	
Level III—				
Two normal brains		0·462		0·483 = Average 0·473
Senile chorea	Case 2		0·439	

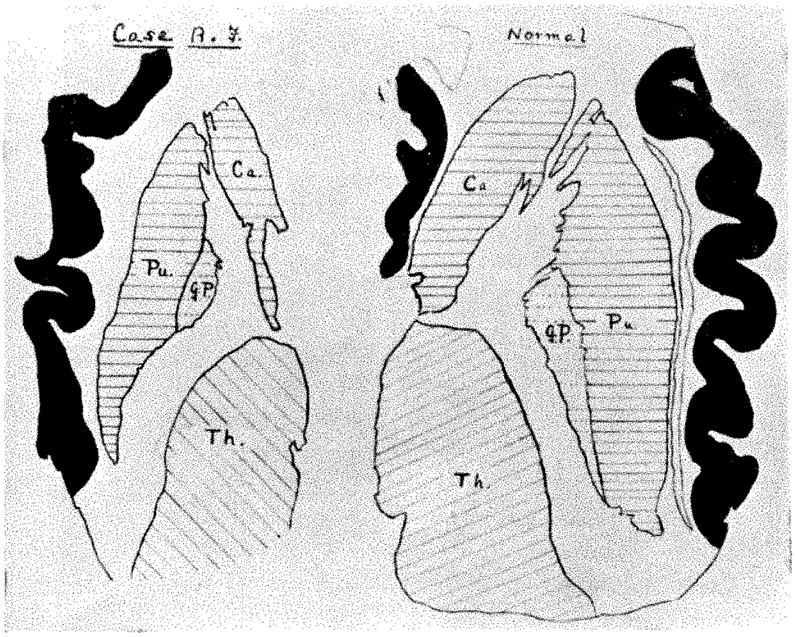

FIG. 1.—The outline of one of the sections of Case 1 for comparison with the drawing of a section through a normal brain at the same level.

PLATE VI.

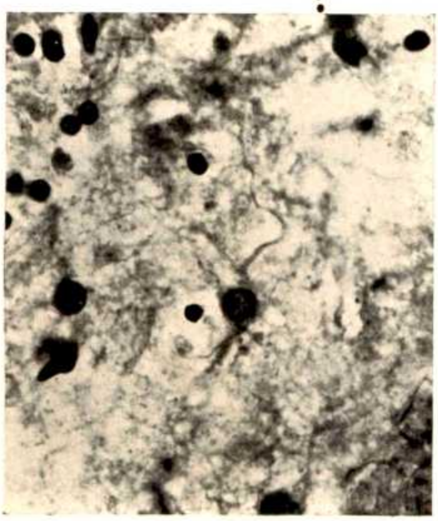

FIG. 1.

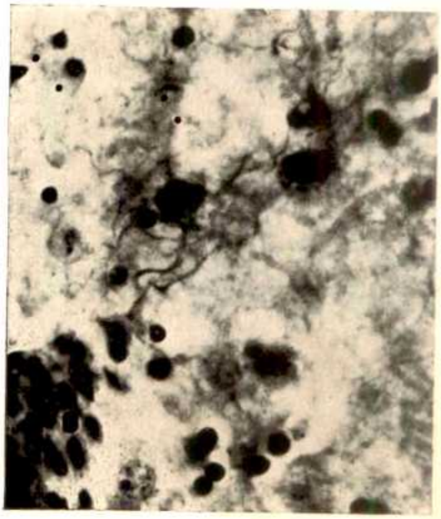

FIG. 2.

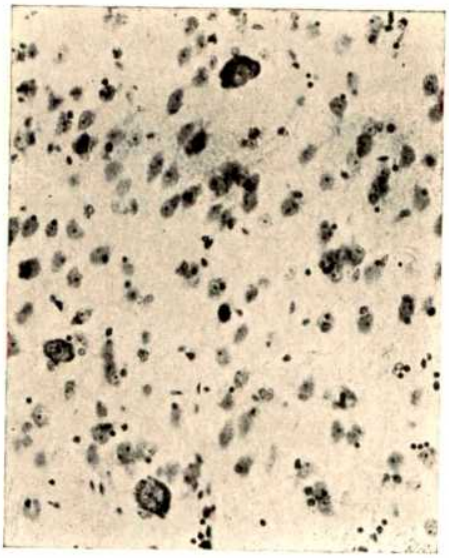

FIG. 3.

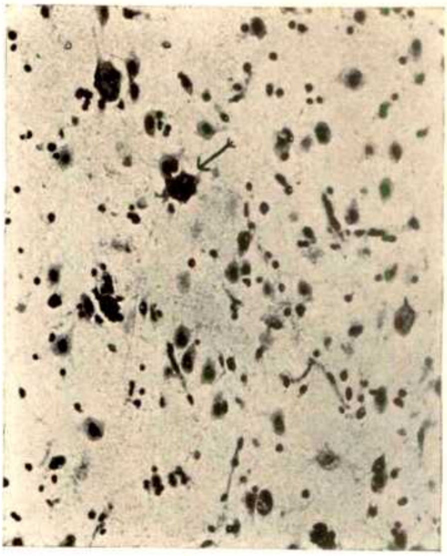

FIG. 4.

FIGS. 1 and 2.—Sections of caudate (fig. 1) and putamen (fig. 2) from Case 1. To show the fibrous astrocytes. Stained by Mallory's phosphotungstic acid hæmatoxylin method. × 500.

FIGS. 3 and 4.—Section of caudate from a normal case (fig. 3) and from Case 1 (fig. 4). To show the degeneration and reduction in number of large and small nerve cells. The arrow points to a large degenerated cell which is packed with pigment. Stained by Nissl's method. × 200.

To illustrate paper by N. S. Alcock.

MICROSCOPICAL APPEARANCES.

Case 1.—*The Putamen.*—The nerve-cells showed a marked reduction in number: although no cell counts were made, there was no doubt about this. In a normal putamen, in an ordinary field under high power there are always numbers of small cells and one or two large cells, the small cells being, of course, considerably in excess of the large ones. In this case there was only an occasional small cell and several fields had to be searched for a large cell.

The incidence of the affection varied a little from place to place although the difference was not very great. If anything the posterior two-thirds of the putamen tended to show the greatest pathological change.

The appearance of the cells themselves was also greatly altered. The great majority stained poorly, especially with Nissl's method, and their edges were ill-defined. This again varied somewhat from cell to cell; some stained so poorly that they might justifiably be called "shadows," and sometimes the degeneration was so advanced that it became almost a guess that the structure had been a nerve-cell.

An occasional cell, particularly a large cell, had become packed with pigment so that its internal structure was not visible. Such a cell can be seen in the microphotograph of Case 1 (Plate VI, fig. 4). The nuclei also stained poorly and were often eccentric and larger than normal.

These appearances were present in both the large and small cells and it was particularly noted that both were about equally affected. The impression gained from studying several sections was that there was a similar reduction in number of large and small cells.

The neuroglial nuclei were more numerous than in the normal sections, and their marked increase seemed more than could be accounted for by the shrinkage in the size of the whole putamen.

The astrocytes here were particularly interesting. Several of these showed a nucleus and long branching processes which stained well by Mallory's phosphotungstic acid hæmatoxylin method, i.e. the fibrous type of astrocyte. These are not a normal constituent of the putamen, and their presence bears out the contention that there is more change in the glial cells than could be accounted for by shrinkage. (Plate VI, figs. 1 and 2.)

The caudate nucleus.—The pathological changes here were similar to those described in the putamen, but they were less pronounced in its lower part. The upper part of the nucleus was equally severely affected.

There was a similar reduction in number and the same poorly staining degenerated appearance was seen in both the large and small nerve-cells.

The glial changes were also found here, and there was a much greater number of the "spider cell" astrocytes. In the normal caudate there is an occasional fibrous astrocyte near the wall of a blood-vessel and a fairly dense network of these cells line the wall of the ventricle. The same emphasis on their presence does not apply therefore. They were, however, so much in evidence that in the upper part of the caudate in Case 1 the appearance was almost that of a glial scar.

The globus pallidus.—A sudden change of picture is found here. The nerve-cells, which are all large ones, are well stained and had sharp clearly defined edges. Their nuclei which usually lay near the centre of the cell stained normally.

They are obviously more per field than in the normal globus pallidus. This fact and their uniformly healthy appearance leads to the conclusion that the apparent increase in number is accounted for by the shrinkage in the total size of the ganglion.

No pathological change could be seen in the neuroglial elements, beyond a similar increase in their number per field.

Sections stained for myelin on the whole showed very little deviation from the normal. The ansa lenticularis, Forel's H2 bundle, and the fibres crossing the internal capsule from the basal ganglia were all well stained. In some of the sections the ansa appeared a little pale, but this was hardly more than the normal variation from slide to slide.

The only fibres which seemed definitely paler than normal were those that cross the internal capsule lateral to the globus pallidus. These are the only fibres that appear to come from the putamen without first traversing the globus pallidus, and they are normally thinner and paler than the fibres which cross the internal capsule more mesially. In view of this normal variation it is difficult to be certain of the degree of pathological change.

Cerebral cortex.—In the sections studied there was no gross alteration in the appearance of the nerve-cells, and apart from an occasional cell that had not taken up the stain perfectly, they were uniformly healthy in appearance. There was also no alteration in the architecture of the various layers, in fact one would pass the cortex as within normal limits.

The thalamus, corpus Luysii, substantia nigra, mid-brain, pons and cerebellum were studied, the corpus Luysii particularly in view of the cases in which a lesion of this nucleus is associated with hemi-chorea; but no pathological change was seen in their cells as compared with the normal.

The blood-vessels.—In places these showed some thickening of the wall, but there was no gross change in either case. There was no marked atheroma and no perivascular infiltration of cells.

Case 2.—As has already been noted in this case there was less shrinkage of the basal ganglia. In the putamen, however, there was again a marked reduction in the number of both small and large nerve-cells. Although this reduction was not quite so marked as in Case I the impression was obtained that there was more similarity between the microscopical appearance than would have been expected from the macroscopical picture. Both the large and small cells presented the same degenerated appearance. In this case also no cells were visible that could be regarded as really normal. The globus pallidus contained healthy cells, which seemed to be relatively increased in number in the section.

There was not such a marked increase of neuroglia, but again fibrous astrocytes could easily be found both in putamen and caudate.

Outside the caudate and putamen there was no difference worthy of remark between Case 1 and Case 2. Within these nuclei the changes were merely those of degree. In Case 2 they were not so marked as in Case 1, but the pathological affection seemed to be the same in quality if not in quantity.

Unfortunately the clinical notes do not allow the comparison of the degree of the chorea, and it could not be ascertained whether the chorea in the second case reached the degree it did in the first case. Presumably the more severe histological changes in the first case correspond with the greater degree of shrinkage of these ganglia.

DISCUSSION.

If cases of chorea with mental changes, or with a family history of chorea or mental changes, are excluded, senile chorea is a rare disease. In its early stages the disease progresses, and although it tends to become stationary, the term "chronic progressive chorea" would apply to these cases; but unfortunately this term has been indiscriminately applied both to this condition and to Huntington's chorea, and therefore the term "senile chorea" is to be preferred.

In two conditions in which the chief symptom is so similar, it is to be expected that the pathological picture would also be similar, and this is what is found. In both conditions there is a gross shrinkage of the basal ganglia. The degree of this varies with the case, but in senile chorea it is not so marked as that found in Huntington's chorea. On an average of the figures, expressed as percentages of the normal, we find that the putamen in senile chorea gave measurements of 45·8 and 72·3 per cent., while in Huntington's chorea it gave 42 per cent.; the caudate in senile chorea gave 54·6 and 77·3 per cent., while in Huntington's chorea it gave the figure of 49 per cent. The globus pallidus gave 75·8 per cent., while in Huntington's chorea it gave 72·75 per cent.

It is interesting to compare the figures obtained by this method with those obtained by Dunlap [6], who made plaster models of the whole of the lenticular nucleus and found this structure in Huntington's chorea as 1 : 2·3 of the normal, i.e. 43·5 per cent.

There is no significant difference between the size of the thalamus in the normal and in senile chorea or Huntington's chorea. This is what would be expected from the normal microscopical picture of the thalamus in these conditions.

As a summary, therefore, we can say that in the basal ganglia, senile chorea shows changes similar to, but of a less degree, than those found in Huntington's chorea. That the various nuclei are affected in the same order; but in each it is a less intense affection.

The chief difference in the microscopical findings between the cases, is that in Huntington's chorea there are pathological changes in the cortex which are not present in senile chorea. This supports the generally accepted view that it is these changes that are responsible for the mental changes in Huntington's chorea, which are absent in senile chorea.

In the basal ganglia the condition is very similar. In both there is a marked affection of the cells of the caudate and putamen. These changes appear to be degenerative in nature, as many of the cells disappear altogether and the remaining ones all show considerable change. The changes tend to be less extreme in senile chorea, which perhaps corresponds with the less progressive nature of the affection. It is noted that although the pathological changes vary from cell to cell, on the whole the incidence is fairly uniform, and that the large and small cells are equally affected.

There is also an overgrowth of the neuroglia in response to these changes, which is shown firstly by the increase in their number and more conclusively by the appearance of types, such as the fibrous astrocytes that are not usually present in this region of the brain.

In the globus pallidus the nerve-cells are unaffected, and it seems therefore reasonable to suppose that the shrinkage in the size of the globus pallidus is due to the degeneration of fibres which normally come from the nerve-cells of the putamen.

The microscopical appearances thus bear out the assumption that senile chorea is dependent on changes similar to those present in Huntington's chorea, but that the process is less advanced. This corresponds with the relative diminution in size of the putamen and caudate nuclei as revealed by measurement. There is, however, the significant difference in the cortex which is unaffected in senile chorea.

On these grounds therefore it is justifiable to separate senile chorea as a pathological as well as a clinical entity from Huntington's chorea.

Ætiology.—We can exclude syphilis as an ætiological factor in these cases, and there is no evidence of a vascular basis for this condition, for no disease was found in the blood-vessels, and in any case a lesion that is so localized does not suggest a widespread cause like vascular disease.

We know that the basal ganglia tend to be affected in certain general diseases, such as hepato-lenticular degeneration in which Wilson [7] suggested an unknown toxin originating in the liver. There is no evidence of any disease of the liver in senile chorea, but it may be that these cases have a toxic origin. There is, however, no evidence in favour of this view, and it appears better to consider them simply as a system degeneration. Whatever the cause may be, it is reasonable to assume that one physiological system is affected.

As both the large and the small cells of the putamen are affected, while those of the globus pallidus escape, it would appear that there is a closer alliance between the large and small cells of the putamen than between the large cells of the putamen and the cells of the globus pallidus. Ramsay Hunt [8] has suggested that the small cells in the putamen belong to one system, and that the large cells in the putamen and in the globus pallidus belong to another, and that with an affection of each system, a particular set of symptoms appear. That disease of the small cells is associated with chorea; of the large cells with striatal rigidity.

Neither the cases of senile chorea nor those of Huntington's chorea support this contention, for it appears improbable that part of the system would show such marked change while the rest appears perfectly healthy.

Additional evidence is afforded by the fact that these cases, and particularly the cases of Huntingtonian chorea, may advance to extreme degrees without showing any lesion in the cells of globus pallidus. The suggestion that all the cells of the putamen are one system and those of the globus pallidus another is supported by Davison [4] and by Winkleman [9] in his discussion on Davison's paper.

The efferent tracts from the basal ganglia consist of the ansa lenticularis, Forel's H2 and the fibres crossing the internal capsule. The ansa and Forel's bundle both appear to come from the globus pallidus and go to the region of the red nucleus, the substantia nigra, the corpus Luysii and neighbouring areas. In the cases I have investigated they do not show any signs of degeneration, and this is additional evidence that they do not come directly from the cells of the putamen.

The fibres that cross the internal capsule may be divided into two parts, the more medial appear to come from the globus pallidus, while the more laterally placed come from the lateral part of the putamen where it is in direct relationship with the internal capsule. These fibres go to form the capsule of the corpus Luysii, and it is these that appear to be paler than normal in the two cases of senile chorea described.

This may be of interest in view of the fact that lesions of the substantia nigra—as in chronic encephalitis lethargica—are associated with the clinical state of Parkinsonism, while lesions of the corpus Luysii are associated with chorea.

The changes in the myelin-stained sections are, however, slight in relation to the changes in the cells, and this would confirm the impression that the chief efferent connections of the putamen, except perhaps those associated with the fibres described, are with the cells of the globus pallidus.

It may be suggested that the incidence of the affection is at one level of the extrapyramidal system, and that this level is represented by the small and large cells of the caudate and putamen, while the other levels, such as the globus pallidus, substantia nigra and other parts of the basal ganglia, are unaffected.

SUMMARY.

(1) Two cases of senile chorea are described with pathological findings.

(2) A new method of mensuration is described.

(3) Comparisons and differences are drawn between Huntington's chorea and senile chorea, and it is suggested that there is sufficient evidence to regard them as different entities.

(4) It is suggested that the small and large cells of the caudate and putamen belong to a different system from those of the globus pallidus.

My thanks are due to Dr. F. M. R. Walshe and Dr. J. Purdon Martin, who have allowed me to use their cases. To Dr. J. G. Greenfield in whose laboratory the work was done, and who throughout gave many suggestions, and to Dr. E. A. Carmichael, who also kindly gave advice.

REFERENCES.

[1] Collier, J., and Adie, W. J. Price, "A Textbook of the Practice of Medicine," London, 1935.

[2] Brain, Russell. "Diseases of the Nervous System," London, 1934.

[3] Critchley, M. *Lancet*, 1931, **1**, 1221.

[4] Davison, C., Goodhart, S. P., and Shlionsky, H. *Arch. Neurol. and Psychiat.*, 1932, **27** 906.

[5] Jakob, A. "Der amyostatische Symptomenkomplex u. verwandte Zustände." *Deut. Zeischr. f. Nervenh.*, 1922, **74**, 47.

[6] Dunlap, C. B. *Arch. Neurol. and Psychiat.*, 1927, **18**, 867.

[7] Wilson, S. A. K. Brain, 1912, **34**, 295.

[8] Hunt, J. R. *Arch. Neurol. and Psychiat.*, 1934, **30**, 1332; Brain, 1917, **40**, 58.

[9] Winkleman, N. W. In discussion on ref. [4]; *Arch. Neurol. and Psychiat.*, 1932. **27**, 1.

NOTICES OF RECENT PUBLICATIONS.

Handbuch der Neurologie. Herausgegeben von O. BUMKE und O. FOERSTER. Berlin: Springer, 1936.

The last three volumes of this system of neurology which have been received attain the high level of their predecessors.

BAND IV: *Hirnnerven und Pupille.* S. 701, mit 173 Abbildungen. Price RM. 135.

Short articles by Riese on disturbances of smell by lesions of the olfactory bulbs and olfactory cortex open this volume. Marchesani contributes a full and comprehensive chapter on diseases of the optic nerves, including papillœdema and retrobulbar neuritis. The two latter conditions are discussed at length, especially with reference to their differential diagnoses. Jaensch's chapter on the investigation of visual function is clear and adequate for the neurologist; he also contributes an excellent article on the pupils. The disturbances of the ocular movements, which was undertaken by Bielschowsky, is perhaps the most striking contribution to the volume; the palsies, ataxias and spasms of the associated movements, as well as the effects of lesions of the oculo-motor nerves, are discussed in a masterly manner, and the subject is presented concisely and clearly. Disorders of vestibular function are demanding more attention in neurology as the important part they play in various reactions of the body is realized, but Klestadt's article of 300 pages on the affections of the nervus acusticus is perhaps out of place in a textbook of this type, although it presents the subject very well. The 20 pages allotted to affection of the other cranial nerves is proportionately meagre.

BAND V: *Rückenmark, Hirnstamm, Kleinhirn.* S. 639, mit 345 Abbildungen. Price RM. 123.

The diseases of the spinal cord and its roots are dealt with by Foerster in the first 400 pages of this volume. It is mainly with the effects of local lesions that he deals, as the systemic and pseudo-systemic diseases are described elsewhere. Every section includes the essential facts of anatomy and physiology; in fact a striking feature of this article, which adds so much to its value, is the presentation of symptoms as disturbances of normal functions. In addition to the motor and sensory disturbances, the disorders of the vegetative system, the reflex disorders and the inco-ordinations and the morbid synergias which result from spinal lesions are fully discussed. The only criticism which can be raised is the absence of reference to recent work on the bladder and rectum and their sphincters. Lotmar deals with the symptoms associated with disease of the basal ganglia, and Környey with those due to lesions of the brainstem and thalamus. A short but comprehensive and up-to-date article on the symptomatology of the hypothalamus is contributed by Gagel, and Stenvers writes on the postural reflexes. The volume ends with a chapter by Marburg, which might have been profitably lengthened, on the symptoms of cerebellar disease.

BAND X. *Erkrankungen der Wirbelsäule des Schädels mit Nebenhöhlen und der Hüllen.* S. 465, mit 105 Abbildungen. Price RM. 92.

This is a particularly important volume as subjects which often confront the neurologist, but are usually neglected in smaller textbooks, are dealt with excellently here. Lange describes both the commoner and rarer affections of the vertebral column, and Antoni writes on the primary and metastatic tumours involving it. These articles are excellently illustrated. Affections of the scalp and skull are undertaken by Schulze, and Hirsch deals with the intracranial complications of infections of the accessory sinuses. Brunner, a well-known authority on the subject, discusses the intracranial extension of infections from the ear, including cerebral abscesses. Pette contributes a long article on pachymeningitis and leptomeningitis, the most interesting section of which is that on arachnoiditis. The volume ends with an article by Ehrenberg on subarachnoid hæmorrhage.

Pathology of the Nervous System: A Student's Introduction. By J. HENRY BIGGART. Edinburgh: E. and S. Livingstone. 1936. Pp. 335 with 204 illustrations. Price 15s.

This little book makes no claim to be a complete textbook of neuropathology, but rather to replace and amplify the section on the nervous system in the average textbook of pathology, and to relate this branch of pathology to general pathology. In this it is very successful. The chapter on the neurone is perhaps the most disappointing, as it is too short and condensed to allow of adequate description of the various types of change in the nerve cell, or of the processes of degeneration and repair in the nerve fibre. The other chapters are full enough for their purpose, and those dealing with general processes such as vascular disease and inflammation are excellent. Throughout the book the macroscopic appearances are well described, and questions of pathogenesis in the various diseases are not neglected. The chapters on cerebral and spinal tumours are specially good, and the illustrations here are excellent. Indeed the book is well illustrated throughout both with photographs and drawings. As a whole the book compares very favourably with similar books on neuropathology which have recently appeared in the United States and is very much cheaper.

An Inquiry into Prognosis in the Neuroses. By T. A. Ross. Cambridge: The University Press. 1936. Pp. 192.

It is rare to find a completely dispassionate review and assessment of any mode of medical or surgical treatment, and to seek for it in the literature of the neuroses might seem a singularly unpromising enterprise. Nevertheless, despite the difficulties inherent in the task, Dr. Ross has accomplished it with a remarkable degree of success, and in doing so has laid his professional brethren under a debt of gratitude. In the chaos of conflicting speculations and therapeutic claims that go to swell the monstrous bulk of medical psychological literature, it has become virtually impossible for the ordinary medical reader to separate the grain from the chaff, but in this review of 1,200 cases which have come under his personal observation, Dr. Ross has provided us with a standard by which we may hope to form a reasonable view of the results which skilled and judicious treatment may obtain in the neuroses.

This large series of cases represents the practice of the Cassel Hospital for Functional Nervous Disorders during the period in which Dr. Ross was its Medical Director. His "inquiry" is a model of what such an investigation should be. It cannot be summarized, but one or two striking conclusions may be cited from it:—

(i) Short courses of treatment in which there is no exploration of the infantile unconscious and no formation of a transference which had to be resolved, may be sufficient to bring about character changes of a kind followed by durable improvement in health, and this in other than trivial conditions.

The tacit assumption that anything short of Freudian analysis is useless, is not true.

(ii) The nature of a neurosis does not afford certain evidence as to whether short, or prolonged and analytic treatment will be required.

Each of the main varieties of neurosis is discussed separately, and there are a large number of statistical tables and case histories appended.

This book may be most warmly commended to the attention of neurologists and those psychotherapists who are not neurologists.

The Cerebrospinal Fluid and its Relation to the Blood. By Solomon Katzenelbogen. Baltimore, 1935. The Johns Hopkins Press. Pp. 468. Price 22s. 6d.

This fully documented work covers every aspect of the subject in a full and yet concise manner. The enormous amount of literature which has appeared of recent years is shown by the 44 pages of references at the end of the book, and the author's task in summing up the evidence thus collected must have been a very arduous one. As might be expected from its title, the relation of the chemistry of the spinal fluid to that of the blood forms the chief subject matter and the physical bases of the formation and absorption of the cerebrospinal fluid are only briefly surveyed. Within this limited field the book is remarkably complete, and any omissions of recent important work are readily explained by the time needed to compile the book. The only criticism that can be made is that the evidence might have been more critically sifted and the author might have used his own judgment more freely in rejecting observations which are either out of date or obviously erroneous. The data given are, however, so abundant that it is usually possible for the reader to correct this fault; if indeed it be a fault to give an observer the benefit of the doubt when it is impossible to check his results. There are also short summaries to many of the chapters in which the author sums up the evidence with a wisdom born of wide experience and intensive research. A comprehensive review of the subject, such as this, will be of great value to those who take a scientific interest in the cerebrospinal fluid.

Handbuch der Biologischen Arbeitsmethoden. Herausgegeben von E. Abderhalden. Urban und Schwartzenberg: Berlin, 1935.

Experimentell-psychologische Schwachsinnsdiagnostik von E. Stern. Abt. VI. Lieferung 448. S. 188. Price RM. 11.

Analyse des Willens. von N. Ach. Abt. VI. Lieferung 446. S. 460. Price RM. 22.

In his preface to the volume in which Dr. Stern's monograph appears, Prof. Abderhalden remarks that there are plenty of problems in applied psychology but no scientific methods which can be used for attacking most of them. This objection does not apply to Dr. Stern's subject which has been carefully investigated by clinical observers and psychologists in many countries. English research is, however, overlooked in this book, e.g. the perceptual tests worked out under Spearman's influence are not mentioned, and the copious American studies receive only the scantiest attention. Apart from this the work is a critical and well arranged guide to intelligence testing and other psychological means of diagnosing mental defect.

Prof. Ach's contribution is on a topic with which his name has been pre-eminently associated for thirty years. Those who have no use for the concept of volition because of their belief in psychological determinism will find here many stubborn experimental facts. Ach's familiar methods of studying the influence of a set task upon the mental processes are fully expounded, with careful discussion of the different viewpoints. The highly technical presentation begins with a general review of the problem and the value of self-observation in studying it: the remaining six chapters deal minutely with "the determining tendency," automatization, monotony, motivation of volitional acts and other subtle questions. It is a book for the expert.

Prognose und Therapie der Geisteskrankheiten. von Max Muller. Leipzig: Thieme. 1936. S. 164. Price RM. 7.20.

This is essentially a compendium in which the more recent publications in the German language are reported and arranged in appropriate chapters. The defects of the work may be seen in the section on syphilitic psychoses, in which not a single English or American investigation is mentioned. The author is an enthusiast about treatment, as his earlier work on the curative mechanisms in schizophrenia had shown. The sections on prognosis are meagre. The author's own views are chiefly given in the chapter on individual psychotherapy, where psychoanalysis is described as the method of choice, with suggestion as a poorer, though often sufficient, alternative and supplement. Among the special chapters are two on epilepsy and drug addictions, but none on the psychoneuroses.

Intelligence, Concrete and Abstract. A Study in Differential Traits. By W. P. ALEXANDER. London: Cambridge University Press. 1935. P. 177. Price 12s. 6d.

The use by Spearman and his pupils of the tetrad method has resulted in much analysis in terms of group factors, but so far no conclusive attempt has been made to resolve performance tests in this way. Dr. Alexander has tried in a painstaking statistical research to remedy this gap in applied psychology. His investigations were made on English and American schoolchildren of various ages and on delinquent women. He concludes that there are factors concerned with practical ability, persistence and the use of numbers, which play an important part in achievement of tasks not predominantly verbal, and he offers in an appendix a suggested use of the tests to measure practical ability. The chief bearing of his research is on education and vocational guidance.

Experimentelle Psychologie in Demonstrationen. von E. BRUNSWIK. Wien: Julius Springer. 1935. S. 166, mit 135 Abbildungen. Price RM. 10.60

The chief merit of this course in experimental psychology lies in the success with which it avoids the use of complicated apparatus. The experiments are designed to give a general survey of the rules and methods of modern psychology, but they will strike the medical reader as cavalier in their treatment of the educational, clinical and social aspects, e.g., the section on "feeling" and emotion is meagre, as is that on intelligence tests. The work is in short academic, but, within its limitations, useful and clear.

The Self in Psychology: A Study in the Foundations of Personality. By A. H. B. ALLEN. Psyche Monographs No. 5. London: Kegan Paul. 1935. Pp. 282. Price 10s. 6d.

The author of this work is widely read in the contemporary literature of psychology but shows limited acquaintance with its methods. His treatment of the topic is on dialectic lines, more akin to philosophy than to any branch of natural science. His main argument is that there is an active central factor or "self" present in all mental life, viewed as an "inner" series of conscious and subconscious events in living human beings. The physical or "outer" series of events he deliberately excludes from his survey.

Basic Problems of Criminology. By OLOF KINBERG. London: William Heinemann. 1935. Pp. 436. Price 20s.

This interesting but diffuse work, of which a great part is devoted to theoretical problems of "imputability," will, responsibility, morality and the purpose of penal law, is reflective rather than clinical. The author devotes two chapters to constitutional and environmental causes, and to the medical and biological aspect of criminal behaviour. He instances the effects of encephalitis lethargica and other brain disease upon conduct, especially sexual conduct, and stresses the importance of the endocrine glands, quoting the assertions of Pende, Vidoni, Berman and others with uncritical favour. In a valuable chapter he described the system of examining prisoners in various European and American States, and makes recommendations on this point, also laying down the general principles of treatment which he thinks desirable. The arguments for sterilization as the most effective means of preventing crime are stated in the last chapter of the book with missionary zeal.

Opicinus de Canistris. Weltbild und Bekenntrisse eines avignonesischen Klerikers des 14. *Jahrhunderts.* von R. Salomon. Textband und Tafelband. London: the Warburg Institute. 1936. Pp. 348 and 89 plates.

The influence of cultural pattern upon the form of mental disorder is well exemplified in the autobiography of Opicinus de Canistris, now for the first time published since it was discovered by Saxl in the Vatican Library in 1913. The autobiography, which has great psychiatric interest, is only one of about two dozen pages of parchment, here beautifully reproduced in the accompanying volume of plates, in which the Pavian cleric gave symbolic and pictorial form to the contents of his mind. The mental disorder under which he laboured when he drew them seems to have been a severe self-reproachful depression, but his productivity was not notably lessened, and there are obsessional and schizophrenic features also. Dr. Salomon's very erudite description and commentary provided the material for a detailed analysis of the structure of this psychosis, so far as it depends on an understanding of the cultural milieu in which the writer lived. There are appended to the main volume a learned examination of the Pavian's artistic method and sources by Heimann, and a note by Krautheimer on the old double cathedral of Pavia which Opicinus has figured. The volume of plates also contains reproductions, a few of them anatomical, from relevant manuscripts and other mediæval works of art.

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EDITOR.

DECEMBER, 1936

BRAIN.

PART 4, VOL. 59.

PITUITARY BASOPHILISM ASSOCIATED WITH A BASOPHIL CARCINOMA OF THE ANTERIOR LOBE OF THE PITUITARY GLAND.

BY HENRY COHEN AND J. HENRY DIBLE.

(From the Departments of Medicine and Pathology, University, and Royal Infirmary, Liverpool.)

CUSHING'S syndrome of pituitary basophilism has attracted wide attention since its original description in 1932 [1]. In addition to the 14 verified cases included in Cushing's papers and review of the literature, there have since been described at least 20 cases of the syndrome which have come to autopsy. These are analysed in a recent monograph by Jonás [2]. He records 35 fatal cases, including those described by Cushing. The pathological change in the pituitary in 21 of these was found to be a basophil adenoma; in 4 hyperplasia of the basophil elements was described; in 2 a chromophobe adenoma; in 1 an acidophil adenoma; and in 2 " tumours " as yet undifferentiated are reported. In 2 cases the pituitary was said to be " normal " though the nature of the examination was not specified; in 3 cases serial sections of the gland revealed no lesion.

Essentially the same clinical features which characterized Cushing's syndrome have, however, been found in cases in which the primary pathological lesion appears to have been: (1) adrenal cortical hyperplasia or new growth [3] and [4]; and (2) carcinoma of the thymus [5]. Related, and in some respects, strikingly similar clinical pictures have been described in: (3) pineal tumours [6]; (4) gonadal tumours [7]; and (5) a tumour in the interpeduncular space with a normal pituitary body [8].

The work of Susman [9] and others [10] emphasizes, what indeed might have been foretold, that small basophil adenomata may occur in the absence of Cushing's syndrome. There is, however, abundantly convincing evidence in the described cases that the relationship between pituitary basophilism and Cushing's syndrome is causal and not casual, even though many features in its pathogenesis remain obscure. If our search of the literature is complete, the case we record below is unique in that Cushing's syndrome, recognized during life and attributed to pituitary basophilism, was found at autopsy to be associated with a *malignant growth—a basophil adeno-carcinoma of the anterior lobe of the pituitary gland, with metastases in the liver.*

CASE REPORT.

(L. R. I., 1932. 28577). Margaret L., a spinster, aged 50 (referred by Dr. H. W. Taylor of Bolton), was admitted to the Liverpool Royal Infirmary on July 9, 1932.

Her ill-health dated from 1927, when she began to gain weight, suffer from headache, and had noticed her "colour" changing. Hair on her chin, face and lips had been present for over twelve months. For over two years she had suffered from gnawing epigastric pain, pain in the back, and exhaustion on slight exertion.

Her family history was not significant. Her father died at 61 from "lung disease"; he had suffered from recurring hæmoptyses and died seven years after their onset. Her mother died at 45 of typhoid fever, to which disease a brother had succumbed at the age of 36. One sister died at 30 of pneumonia. Two brothers and one sister are alive and well.

The only illnesses from which the patient had suffered were measles and chicken-pox as a child.

Her work involved examination of cotton materials for faults after being turned out by weavers.

She was a life-long teetotaler and non-smoker.

She first observed her red face, brown body and limbs three years previously, and she had noticed that her skin had a withered appearance. Thyroid gland was administered at this time without any improvement. Later, patchy deep brown stains and bruises made their appearance in the lower limbs. Soon after this she noticed pads of fat above her clavicles, back of neck, and armpits, which were painful and tender; and her abdomen began to swell. With this she first suffered from gnawing epigastric pain, never very acute, remaining localized and unrelated to food, meals, bowel movement, exertion or cough, but aggravated by stooping. She had no flatulence, nausea or vomiting. Occasionally she suffered from acute lancinating pains radiating round, the lower right ribs. Her appetite had remained good, but she was constipated.

Two types of headache were described. The first was a constant gnawing occipital ache which had been present for twelve months and was occasionally accompanied by a similar sensation behind the nose and in the throat which sometimes "took her voice away." The second type, of which she had experienced six attacks in the preceding four years, was accompanied by intense bitemporal headache, insomnia and vomiting. With each of these attacks the face swelled and remained puffy for some days.

In June, 1931, she first experienced double vision, though for two years prior to this she had worn glasses because her vision was occasionally blurred. Her first attack of diplopia lasted ten days; subsequent attacks were only of a few minutes' duration, though extreme lateral movements of the eyes were associated with slight diplopia.

For twelve months the hair on her face, particularly chin and upper lip, had been increasing; the growth on the lip was so rapid that she plucked it out daily. For at least two years she had noticed her scalp hair becoming sparse, dry and brittle.

Between August and December, 1931, she had six attacks of momentary unconsciousness which caused her to fall; no typical convulsive movements accompanied the attack, though her friends had observed a few clonic movements in the left arm and leg; no local paresis followed the attacks, though she felt exhausted after them. Weakness in the hip flexors and pain in the back had made rising from a recumbent position difficult.

Prior to December, 1930, her menses were quite regular (3-4/28), though dysmenorrhœa was frequent. Without any marked menopausal symptoms her menses ceased in December, 1930, and did not return.

Between November, 1929, and July, 1931, she gained 2 st. in weight; this was then stationary for six months, but during the past six months she had lost nearly 2 st.

She had occasional thirst; had to rise three to four times nightly to micturate during the past few months and passed copious quantities of pale urine.

Examination. (July 4, 1932).—She was a plethoric type, round shouldered, 5 ft. 9½ in. in height, weighing 10 st. 1½ lb. Her face was puffy in appearance, and had a dusky, cyanosed, brownish-coppery hue; there was no jaundice. She had a well-marked moustache and beard growth; eyebrows and eyelashes were normal; the hair of the scalp and axillæ was dry, short, sparse and inelastic; the pubic hair was of feminine distribution. The skin of the body and limbs was rough and dry, had a fine scaly surface and parchment-like texture; brownish pigmentation, especially of the face, nipples, axillæ, lower abdomen and legs below the knees, was striking, and large subcutaneous ecchymoses were present, especially below the knees and on the forearms where slight injury had produced them. Purplish lineæ striæ were seen on the upper and outer aspects of the thighs and on the lateral abdominal wall; they were present, though less marked, on the anterior folds of the axillæ and the upper arm. There were tender pads of fat above the clavicles and over the vertebra prominens; the abdomen was obese and protuberant; this torso obesity was out of proportion to the relatively sparse limbs. No enlarged lymphatic glands were found, though there was a small scar in the right neck resulting from an old gland abscess many years before. The thyroid gland was not enlarged.

Vision in the right eye was $\frac{6}{18}$ and in the left $\frac{6}{18}$ due to hyperopia; the media were clear; the discs were normal; the retinal arteries showed slight sclerosis and tortuosity but no hæmorrhages or exudate were present. The visual fields showed slight general contraction but no characteristic change. The pupils were equal, central and regular, and responded normally to light, both directly and consensually, and to accommodation; ocular movements were full and no nystagmus could be elicited. Other cranial nerve functions were normal. Apart from slight weakness of the hip flexors, there was no focal paresis, and reflexes, sensation, co-ordination, &c., in limbs and trunk failed to reveal any evidence of a focal nerve lesion.

The heart showed left ventricle hypertrophy; the apex beat was 4½ in. to the left of the middle line in the 5th space and was forceful and diffuse; the aortic second sound was accentuated; the fundamental cardiac rhythm was normal but extra systoles were frequent. The blood-pressure was 180/90, pulse-rate 84; the radial artery wall was moderately thickened. An electrocardiogram showed left axis deviation, auricular extra systoles, and inverted T1 and T2; no block was found but in some records the suspicion of a nodal rhythm was present.

Her tongue was furred but normally papillated; she had an upper and partial lower denture; the remaining teeth were satisfactory; no nasopharyngeal disease was evident. Epigastric tenderness was elicited on abdominal examination but there was no localized rigidity, distension or tumour, and neither liver nor spleen was palpable. Rectal examination showed no pelvic abnormality. The larynx was normal. The lungs showed no evidence of active disease.

The urine was acid, sp. gr. 1006, and contained albumin (0·2 per cent.), sugar (0·4 per cent.); no acetone, no bile pigments and no excess of urobilin were present, many hyaline and a few granular casts were seen, but no blood nor pus cells.

The Wassermann reaction in the blood was negative.

The cerebrospinal fluid was clear, colourless, under a pressure of 100 mm. of fluid with normal response to jugular and abdominal compression; it contained no excess of protein, 1 cell per c.mm. and produced no change in the gold curve; the Wassermann reaction was negative in all dilutions.

The blood calcium was 10·5 mg. per 100 c.c., the non-protein nitrogen 30 mg. per 100 c.c., and cholesterol 250 mg. per 100 c.c.

A *urea concentration test* gave the following result after 15 gm. urea:—

Before urea ..	.. ..	0·98 gm. urea per 100 c c.
1 hour after urea	(105 c.c. urine passed)	1·69 ,, ,, ,,
2 hours after urea	(125 ,, ,, ,,	1·69 ,, ,, ,,

A *glucose tolerance test* after 50 gm. of glucose gave the following result:—

	Blood sugar	Urinary sugar
Before glucose ..	130 mg. per cent	Nil
½ hour after glucose	167 ,, ,,	—
1 hour after glucose	200 ,, ,,	Nil
1½ hours after glucose	176 ,, ,,	—
2 hours after glucose	157 ,, ,,	0·8 per cent. sugar

A *blood-count* showed :—

Hæmoglobin.. ..	94 per cent.		
Red cells	5,120,000		
Size—halometer	7·2 microns		
White blood cells ..	7,500 ..	Polymorphonuclears	63 per cent.
		Lymphocytes	30 ,,
		Monocytes	4 ,,
		Eosinophils	3 ,,
		Basophils	0 ,,

Stained films showed no abnormality of the red cells.

Radiograms.—The pituitary fossa was somewhat irregular in outline and there was marked decalcification of the clinoid processes. The skull showed well marked decalcification (this was true of the whole skeleton) but there were many small focal translucent areas. In addition to osteoporosis, the lumbar spine showed chronic osteoarthritis. No stones were present in the *urinary tract.* No evidence of active tuberculosis nor of an enlarged thymus was seen in the chest radiograms.

Though the blood calcium was normal, on standard diet containing 100 mg. of calcium daily, her *calcium excretion* averaged 600 mg. in the urine and 390 mg. in the fæces for a three-day period; compared with normal this suggests an increase in urinary calcium excretion.

Dr. M. Datnow investigated (August 29, 1932) the Aschheim-Zondek reaction and reported as follows :—

"½ c.c. urine injected subcutaneously into three male and three female immature mice five times morning and evening consecutively: mice killed after one hundred hours showed no change in their genitalia. This suggests that there is no hormone present which will produce any effect on the ovaries, uterus or testes.

"66 c.c. of a fresh specimen of urine was mixed with 240 c.c. of absolute alcohol; a fair amount of precipitate resulted. This was centrifuged off and the deposit treated with 30 c.c. of ether to extract any œstrin that may have been present (anterior pituitary hormone is not soluble in ether). The remaining precipitate was suspended in 11 c.c. of normal saline solution (if there had been any pituitary hormone present this suspension should contain six times as much as is present in the normal urine). Absolute alcohol precipitates anterior pituitary hormone. ½ c.c. doses of the suspension were injected subcutaneously into a series of female immature mice. These showed no genital changes after one hundred hours.

"If there was any hormone present in Miss L.'s urine, it was in quantities very much below what is found in cases where the pituitary is active.

"A specimen of urine was diluted ten times and ½ c.c. doses given to another series of immature mice with a negative result.

"This was done because a very great excess of pituitary hormone inhibits the change in immature mice, and if there was a flood of hormone in Miss L.'s urine, we might have obtained negative results owing to this. The urine from a normal woman in the child-bearing age would have given more change in the immature mice than that of Miss L.

"The urine from a patient at the menopause would have contained very much more pituitary secretion than that of Miss L."

A course of X-ray therapy[1] to the pituitary area was started on July 26, and two months later she reported feeling much better, her headaches especially being less frequent and intense. This improvement in her headache continued throughout 1933. She then relapsed, with gradually increasing weakness, headache, pains in the back, impairment of vision, lethargy and recurrence of her attacks of unconsciousness.

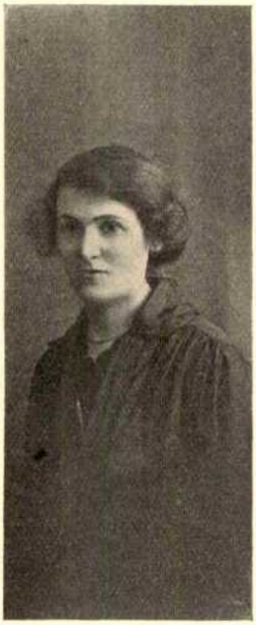

FIG. 1.—Photograph in 1924.

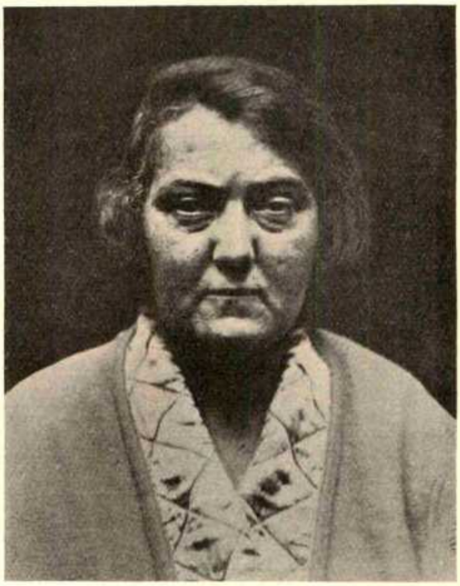

FIG. 2.—Photograph on July 28, 1932.

She was re-admitted to hospital on January 16, 1934. As she was very ill further detailed investigation was not undertaken. Her glycosuria and albuminuria had increased (fasting blood sugar 200 mg. per 100 c.c. and non-protein nitrogen 24 mg. per 100 c.c.) and she had developed an abscess over the left olecranon (probably a suppurative bursitis). A troublesome feature was her severe cough accompanied by considerable mucoid expectoration, slight fever and hoarseness. She had developed an indolent ulcer of the right leg. Later the sputum became purulent but was free from tubercle bacilli. On February 3 she was much drowsier and developed paroxysms of auricular fibrillation; incontinence of urine and fæces appeared on February 4.

---

[1] Treatment commenced on July 26, 1932. Medium Deep X-ray therapy was given at 175 K.V. with ½ mm. copper and 2 mm. aluminium filtration, through two lateral fields 10 by 8 cm. in size centred over the pituitary fossa. The irradiation was carried out by the fractional method, approximately 200 "r" being given to each area at each sitting.

At first the treatment was given once a week for four doses and then at increasing intervals (i.e. once a fortnight for four doses followed by four doses at three-weekly intervals).

On January 11, 1933, treatment was discontinued for two months and recommenced in March, 1933, when the same irradiation was given fortnightly for four months, and finally for two doses at three-weekly intervals. Treatment was discontinued on December 27, 1933.

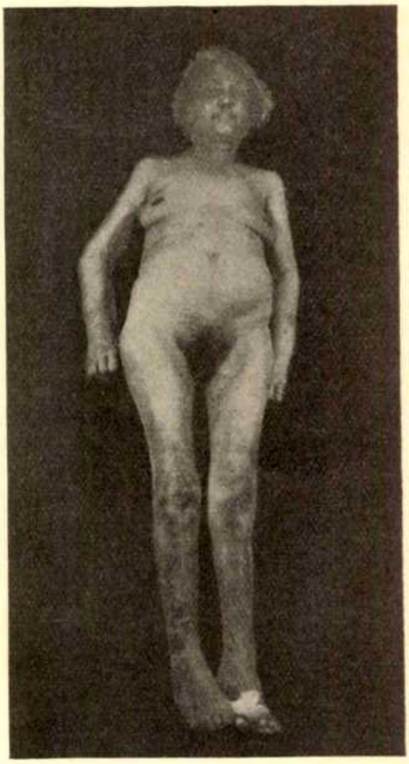

FIG. 3.—Photograph after death showing distribution of fat, hair and pigmentation; lineæ striæ; ecchymoses and ulcer on leg.

On February 8 she fell out of bed and developed marked ecchymoses and crepitus in the right shoulder area, suggesting a fracture of the neck of the humerus. Rapidly developing bronchopneumonia terminated her life on February 11, 1934.

Her extreme reticence prevented our taking photographs of her body during life but her facial appearance in 1924 (fig. 1) contrasts strongly with a photograph on July 28, 1932 (fig. 2). A photograph taken after death shows the characteristic features of the syndrome (fig. 3).

PATHOLOGICAL EXAMINATION.

The post-mortem examination was carried out on February 11, 1934, six and a half hours after death.

The body was that of a small, well-nourished woman, showing the external appearances already described. The skeletal muscles were generally atrophic and showed a good deal of fatty infiltration between their bundles.

Bones.—The ribs were notably decalcified and could be readily cut through with the knife. The condition found was one of simple atrophy of the bone, both of cortex and trabeculæ, without any evidence of fibrous transformation, of the type seen in osteitis fibrosa, or of osteoclastic absorption. There was no histological evidence of the method of removal of the bone. A fracture of the right humerus was present just below the surgical neck and was associated with the same bony atrophy. No similar decalcification, or deficiency in strength, was found in the femora. There was a general hyperplasia of red marrow, this being present in the centres of the shafts of the femora. Microscopically the bone marrow was hyperplastic, the overgrowth affecting all the cellular elements equally.

Circulatory system.—The heart was a little enlarged, weighing 12 oz. The hypertrophy chiefly affected the left ventricle.

Respiratory system.—The upper air passages were healthy. There was a mucopurulent bronchitis. The lungs showed a number of nodules of moderately active caseous tuberculosis at both apices : in other respects they were healthy.

Alimentary tract.—The stomach was healthy. The duodenum showed two diverticula, each about 1 cm. in diameter and depth, situated on either side of Vater's ampulla : these did not show any evidence of inflammatory change. The intestines were healthy. The liver weighed 68 oz. It was the seat of well-marked fatty infiltration and microscopically showed numerous submiliary tubercles. Three or four small whitish nodules of new growth were scattered through it, the largest being 1·5 cm. in diameter. The histology of these metastases will be described in connection with that of the primary growth.

The spleen was about one and a half times the size normal for the subject. It appeared normal to the naked eye. Histologically it showed general congestion and well marked miliary tuberculosis.

The pancreas showed scattered areas of fat necrosis and some general infiltration of the body of the gland with fat. Histologically, however, it showed no noteworthy departure from the normal; the islets being numerous, well developed, and free from fibrosis or fatty infiltration.

Genito-urinary tract.—The kidneys: these were a little enlarged; the right weighed 5 oz.; the left 6 oz. They showed no notable abnormalities. The bladder was the seat of an extremely acute cystitis with bullous gas-infection of the mucosa. The body of the uterus was atrophic. The cervix uteri, however, was relatively enlarged, so that the length of the cervical canal was as great as that of the body of the organ. This enlargement was associated with a marked overgrowth of the cervical mucous glands which presented a quasi-cystic appearance and were filled with thick mucus: the appearance in sections is shown in Plate VII, fig. 4. This relative preponderance of the cervical portion and its richness in racemose mucous glands recalls the fœtal condition. The ovaries were hard, atrophic and fibrous, and showed complete absence of oögenesis or of corpora lutea.

Ductless glands.—Suprarenals: Both glands were enlarged, the right weighing 12·9 gm. and the left 11·9 gm.; this represents an increase of 3 to 4 gm. per gland over the normal. Histologically the enlargement appeared due to an increase in cortical tissue which showed evidence of activity in the shape of numerous hyperchromatic nuclei. There was some deficiency in cortical lipoid which was patchy in its distribution and was associated with the very unusual appearance of neutral fat globules in certain of the cells (Plate VII, fig. 5). In frozen sections stained by Scharlach R., and in those examined by polarized light, it was found that the distribution of this fat was closely associated with that of the anisotropic lipoid, the conjunction of anisotropic substance and neutral fat in the same cells, and their existence chiefly in juxtaposed cells in certain areas being very striking (Plate VII, fig. 6). In view of certain common features which this case presents with those of adrenal virilism we asked Dr. Vines to apply his stain for the specific chromophilic element he has described in the adrenal in this condition [11].

He reported that the reaction was negative.

The thyroid showed a number of small colloid adenomata, the largest being about 1·5 cm. in diameter. In sections the vesicles appeared rather active.

The thymus was not persistent.

The parathyroids were four in number, of average size, and showed no histological abnormalities.

The pituitary was much enlarged and weighed 6·8 gm. It expanded the sella turcica in which the anterior clinoid processes were enlarged and pushed forward. The gland appeared as a dark, plum-coloured, lobulated tumour, which was covered with thin dura mater and which transgressed beyond its fossa and encroached upon the intra-cranial cavity chiefly towards the right side. The stalk of the gland was a little large but appeared normal and was not involved in the growth. It entered the tumour behind and to the left of the main mass. The general view of the growth as it appeared in situ, after the dura had been freed, is shown in the upper and right-hand drawing of fig. 7. The cut end of the stalk is shown in the plane marked 2. The key drawing (Plate IX, fig. 8) shows the appearance of the growth when cut in this plane, the position of the stalk, and the persistence of the pars nervosa, which appears slightly compressed but otherwise intact. The gland also displays a relatively well developed pars intermedia with a number of colloidal vesicles and an intact pars tuberalis.

Histologically the tumour is a carcinoma of the anterior lobe, which in places shows a tendency to a columnar or papillary arrangement (Plate VII, fig. 9). The characters of the tumour cells are definitely basophilic, this feature being especially well shown in sections stained with aniline blue and ponceau de xylidine (a modified Masson's trichromic stain). The cytoplasm is finely granular. The basophilic properties are possibly slightly less pronounced than are those of the basophil cells of the normal pars anterior and the granularity is decidedly finer and less readily visible; if, however, as we believe, these cells represent a malignant overgrowth of the pituitary basophil cell such departures from the normal are only those which would be expected in cells of so highly neoplastic a character. Nor do the cells show the hyalinization which Crooke [12] has described as a constant feature in the basophil cells of the pituitary in cases which clinically show the basophilic syndrome. The conditions are not, however, necessarily comparable, as none of Crooke's observations were made upon malignant cells and, as we have already pointed out, the cells in our case are in other respects dissimilar to the non-malignant basophil cell. The tinctorial characters of the cells are illustrated in the coloured drawings (Plate VIII, figs. 10 to 12), which show the staining properties of the basophilic anterior lobe cells in the normal gland (fig. 10); in a typical area of the primary growth in the present case (fig. 11); and, by contrast, in an acidophilic adenoma from a case of acromegaly (fig. 12).

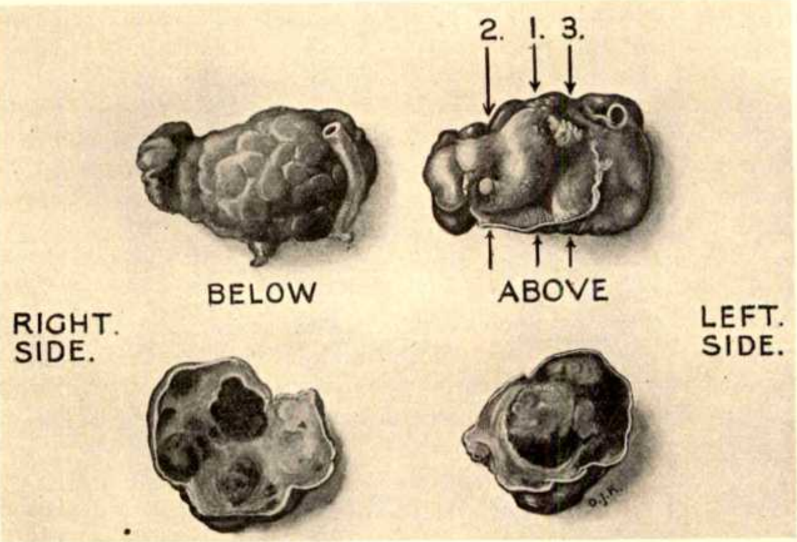

FIG. 7.—Drawing of pituitary carcinoma. Actual size. The interior view is that at plane 1, after removal of a block. The stalk of the pituitary is seen opposite the arrow at plane 2.

The growth in other parts showed a good deal of hæmorrhage and, in general, a well-developed stroma, which in places forms large areas of scirrhous fibrous tissue which is in keeping with a somewhat slowly progressing tumour. A further feature was the presence in separate areas of smaller round cells with large nuclei. Many of these were definitely more chromophil than the large cells figured in the foregoing illustrations. Their significance is not clear, but the fact that they were seen intermingled with the larger cells (Plate VII, fig. 13) in the main growth, and were present in the liver metastases as well, indicates their close connection with the larger type of cell. The liver metastases (Plate VII, fig. 14) faithfully reproduced the characters of the primary growth, the only observed difference being a slightly more anaplastic type of cell with less definitely basophilic and granular cytoplasm.

The survival of some of the normal anterior pituitary elements was clearly seen in a well-preserved pars intermedia and an equally well preserved and developed pars tuberalis which is indicated in the key drawing (Plate IX, fig. 8) and a portion of which is reproduced in the drawing (Plate IX, fig. 15).

From a study of the reported cases the following composite clinical picture of Cushing's syndrome is drawn:—

(1) Obesity—rapidly developing, plethoric, painful, affecting face, neck and trunk but sparing extremities; tender supraclavicular pads.

(2) Hypertrichosis—on face; thinning of hair on scalp.

(3) Amenorrhœa in female; absent libido in male; precocious adolescence in child.

(4) Skin—i. Linæ Striæ—purplish on abdomen, breasts, limbs.
 ii. Pigmentation—dusky cyanosed facies; limbs.
 iii. Ecchymoses
 iv. Acrocyanosis } especially in extremities.
 v. Cutis Marmorata

(5) Hypertension—arteriosclerosis and renal change.

(6) Polycythæmia.

(7) Hyperglycæmia—impaired carbohydrate tolerance.

(8) Osteoporosis—with kyphosis and bone pains.

(9) Asthenia.

(10) Diminished Resistance to Infections—lungs and skin.

(11) Headache, nausea, vomiting, diplopia, visual defects, exophthalmos, lethargy, polyuria, polydipsia, polyphagia—occasionally seen.

Our case showed all but one of these classical features. Polycythæmia was absent. We may, however, point out that a considerable degree of hyperplasia of red bone marrow was found.

The duration of the disease (five years) suggests that the adenoma at the onset might have been benign and that malignant change supervened later. The parts played by the patient's age, and the X-ray therapy in determining this change, cannot be adequately evaluated.

Exact clinical differentiation of the two main causes of Cushing's syndrome—pituitary basophilism and adrenal cortical hyperactivity—is probably impossible in many instances in the present state of our knowledge. The skin changes and osteoporosis, to which differential value has been ascribed, occur in both conditions though less frequently with adrenal growths. Genital hypertrophy with virilism is strong evidence in favour of an adreno-cortical lesion though normal genitalia may accompany adrenal tumours [4]. Radiographic examination, including pyelography and the perirenal injection of air, is often helpful in demonstrating an adrenal tumour; a normal radiogram of the pituitary fossa does not exclude a basophil adenoma.

Cushing adduced strong evidence for ascribing the syndrome primarily to the pituitary gland rather than to the adrenal. Changes in the latter he looked upon as secondary to a primary pituitary basophilism and the case we record might be regarded as adding weight to this view. A detailed study of the literature suggests that even in established cases of pituitary basophilism which are associated with adrenal growths, particularly where there are simple adenomata and cortical hyperplasia, the common sequence is hyperactivity of the basophil elements of the pituitary gland producing adrenal cortical hyperactivity with a resulting Cushing's syndrome. There is at present no evidence to suggest that the sequence: adrenal cortical hyperplasia → pituitary basophilism → Cushing's syndrome is ever seen. But as adrenal growths do give rise to Cushing's syndrome in the absence of any demonstrable change in the basophil elements of the pituitary gland, it seems likely that the syndrome itself is the expression of a disturbed adrenal function, one of the causes of which is pituitary basophilism. At present the relation of Cushing's syndrome which occurs in the recorded diseases of the thymus, pineal body, and sexual glands, to that associated with lesions of the pituitary and adrenal glands remains obscure; but it is of interest to note that in the two cases of cancer of the thymus described by Leyton, Turnbull and Bratton [5] the suprarenal bodies were found at autopsy to be exceptionally large.

SUMMARY.

A case of basophil adenocarcinoma of the anterior lobe of the pituitary gland with liver metastases is reported, which was accompanied clinically by the classical symptoms of Cushing's syndrome.

REFERENCES.

[1] Cushing, H. (*a*) *Bull. Johns Hopkins Hosp.*, 1932, **1**, 137. (*b*) *Journ. Amer. Med. Assoc.*, 1932, **99**, 281. (*c*) Papers relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System. Baltimore, 1932.

[2] Jonás, Vratislav. "Casopisu lékaru ceských, rocník." Praze, 1935.

PLATE VII.

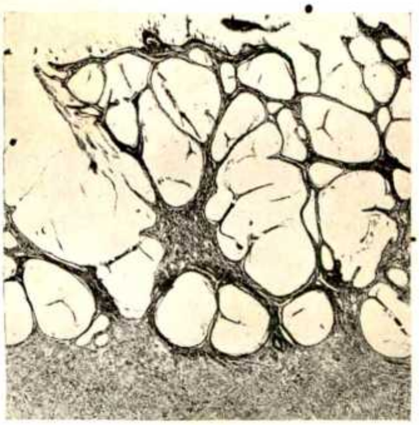

FIG. 4.

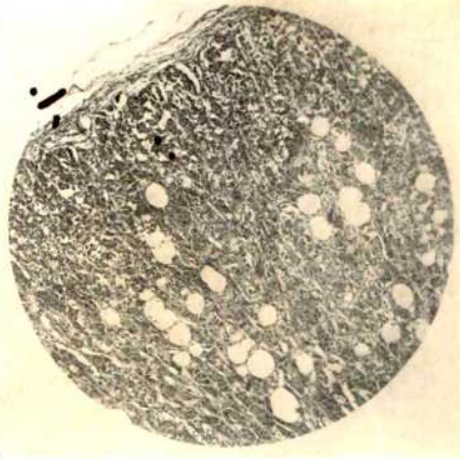

FIG. 5.

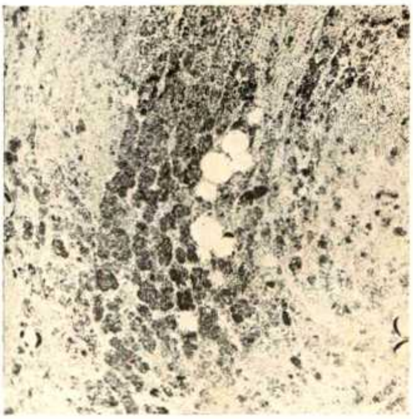

FIG. 6.

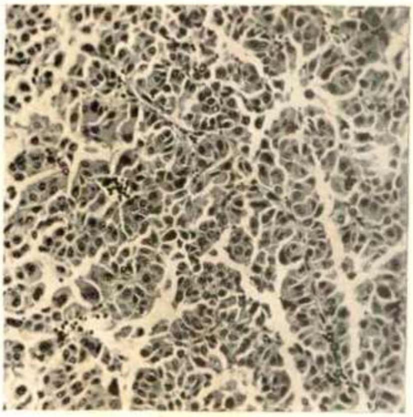

FIG. 9.

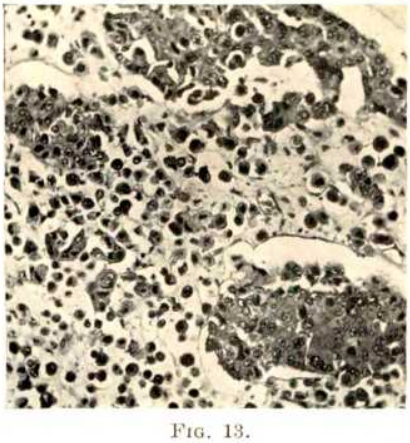

FIG. 13.

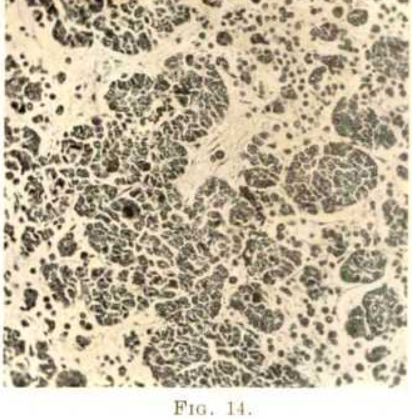

FIG. 14.

To illustrate paper by Henry Cohen and J. Henry Dible.

PLATE VIII.

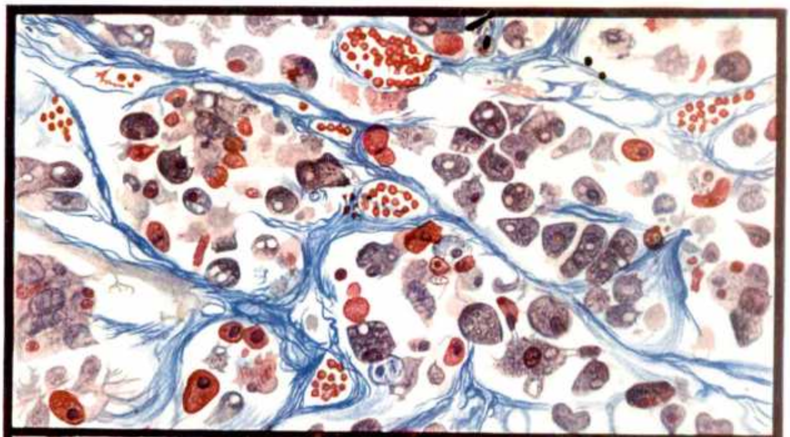

FIG. 10.

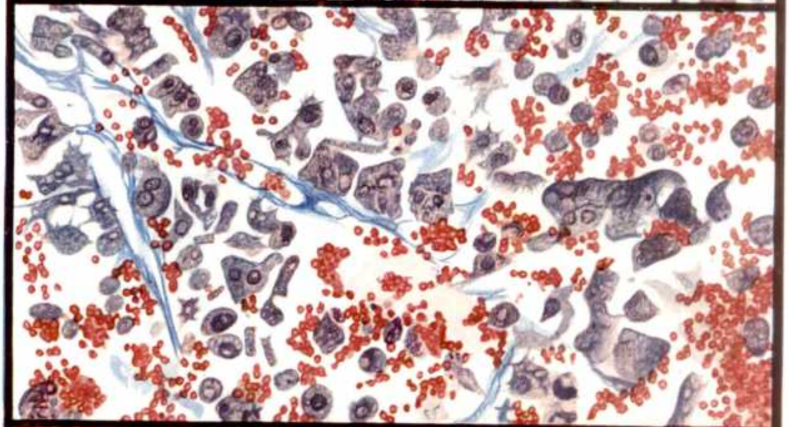

FIG. 11.

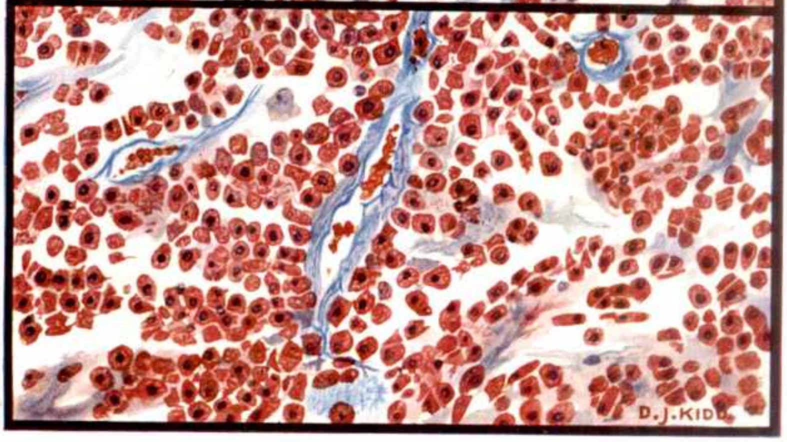

FIG. 12.

To illustrate paper by Henry Cohen and J. Henry Dible.

PLATE IX.

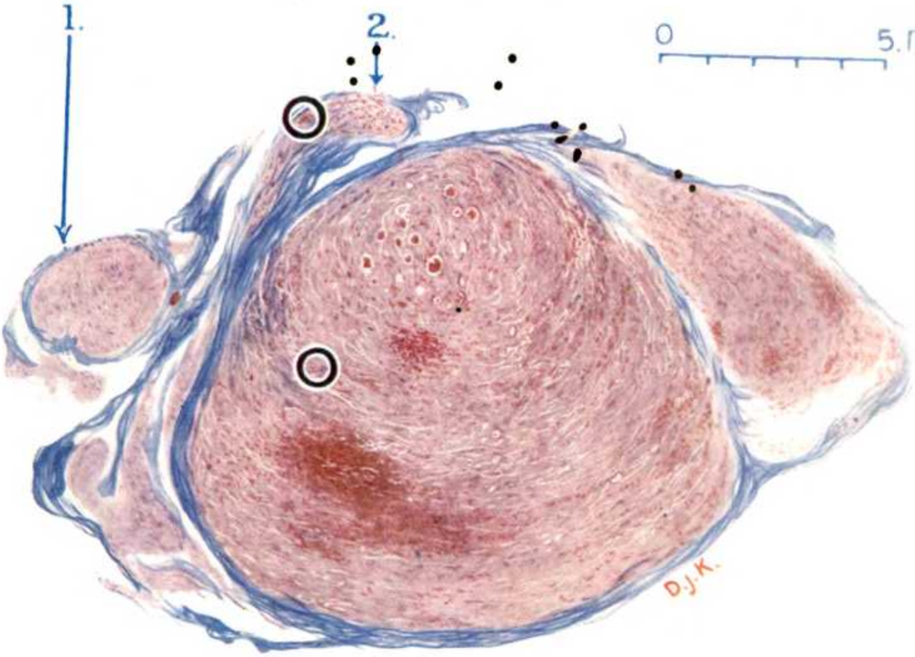

FIG. 8.

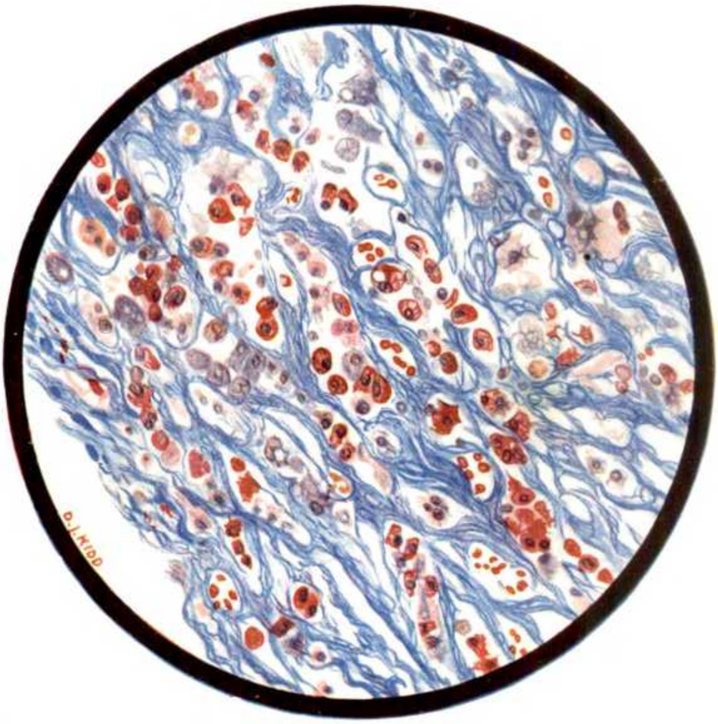

FIG. 15.

To illustrate paper by Henry Cohen and J. Henry Dible.

[3] LESCHER, F. G. *Quart. Journ. Med.*, 1935, New Series, **4**, 23.
[4] CALDER, R. M., and POBBO, F. W. *Bull. Johns Hopkins Hosp.*, 1935, **57**, 99.
[5] LEYTON, O., TURNBULL, H. M., and BRATTON, A. B. *Journ. Path. and Bact.*, 1931, **34**, 635.
[6] ZONDEK, H. "Diseases of Endocrine Glands," 424. Baltimore, 1935.
[7] BÜTTNER, A. *Virchow's Arch. f. path. Anat.*, 1932, **287**, 452.
[8] LE MARQUAND, H. S., and RUSSELL, D. S. Royal Berks Hospital Reports, Reading, 1934-35, 31.
[9] SUSMAN, W. *Brit. Journ. Surg.*, 1934-35, **22**, 539.
[10] WALTERS, W., WILDER, R. M., and KEPLER, E. J. *Ann. Surg.*, 1934, **100**, 670.
[11] BROSTER, L. R., and VINES, H. W. C. "The Adrenal Cortex: a Surgical and Pathological Study." London, 1933.
[12] CROOKE, A. C. *Journ. Path. and Bact.*, 1935, **41**, 339.

LEGENDS TO PLATES VII, VIII AND IX.

FIG. 4.—Cervix uteri showing hypertrophy of the mucous glands. Hæmalum and eosin. × 10.

FIG. 5.—Suprarenal cortex. Certain of the cells show hyperchromatic nuclei. The appearance of large fat globules is a notable feature. Hæmalum and eosin. × 37.

FIG. 6.—Suprarenal cortex. Scharlach stained frozen section showing neutral fat as black globules and clear spaces and anisotropic lipoid as finer granules of a less intense black. × 42.

FIG. 8.—Drawing of tumour (plane 2, fig 7) in the sagittal plane through the stalk of the gland. × 6. 1. Pars nervosa. 2. Stalk. The ringed areas are those reproduced at higher magnifications in figs. 9 and 15.

FIG. 9.—General histology of pituitary tumour. Section from the lower area marked on fig. 8. Heidenhain's iron hæmatoxylin. × 115.

FIG. 10.—Normal pituitary showing an area rich in basophilic cells.

FIG. 11.—The pituitary carcinoma in the present case. A typical field from a section at plane 3, fig. 7.

FIG. 12.—Section of an acidophil adenoma from an acromegalic. All stained aniline blue and ponceau red.

FIG. 13.—Primary growth, section from plane 3, fig. 7, showing large and small types of cell. Hæmalum and eosin. × 115.

FIG. 14.—Secondary growth in the liver. Characters similar to those shown in fig 13. Hæmalum and eosin. × 120.

FIG. 15.—Normal anterior pituitary cells of all types in surviving pars tuberalis—the upper ringed area in fig. 8. Aniline blue and ponceau red.

EXTRAPYRAMIDAL ACTION FROM THE CAT'S CEREBRAL CORTEX: MOTOR AND INHIBITORY.

BY SARAH S. TOWER.

(Department of Anatomy, Johns Hopkins University.)

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INTRODUCTION.

THAT the so-called motor area of the cerebral cortex has inhibitory as well as excitor action, has long been recognized. Inhibition is integrated reciprocally with the dominant motor function, and was studied by Sherrington as an example of that relationship. Yet such inhibition may well be less a discrete component in the total of cortical activity than a condition of action at segmental levels. Some earlier experiments of Bubnoff and Heidenhain (1881) had, however, already demonstrated inhibitory action on the part of the cortex seemingly independent of motor function. After producing a contraction in skeletal muscle by cortical stimulation, these investigators then reduced the strength of their stimulus, and from the same spot relaxed the residuum of the contraction without further motor result. Similarly, Hering and Sherrington (1897) noted that although inhibition of one muscle generally accompanies excitation of its antagonist on cortical stimulation, yet the relaxation of the one precedes the contraction of the other, and with weak stimulation may be obtained alone.

During the course of a study of threshold in the motor cortex (Tower, 1928), the author became convinced that the lowest threshold action of the part is inhibitory—not motor—whenever the presence of a background of tonic contraction in the musculature allows inhibition to be manifest. Later (Tower, 1935), severing the corticospinal tracts below their last large suprasegmental connection, with the pons, was found to dissociate a powerful cortical inhibitory action on tonic contraction in the skeletal musculature from the dominant corticospinal motor function, thus rendering the former accessible to study by ordinary technique for cortical stimulation. At the same time fragments of a novel motor activity came into view. The present investigation was then designed to survey the full scope of cortical extrapyramidal action thus uncovered. In addition to the inhibition of tonic contraction already reported, a second strong inhibition effective against movement has been found, together with a variety of motor activities resembling, in part, those recognized as extrapyramidal by Foerster (1931) in the cortex of man.

Primarily, this study deals with activity which is unequivocally extrapyramidal—activity which is obtained from the spinal cord after both pyramids are cut. Since in the cat no fibres have ever been described passing from the cortex to the cord other than through the medullary pyramids, except in Probst's (1901) instance of gross anatomical anomaly, this distinction between pyramidal and extrapyramidal action is also that between direct cortico-segmental action and action upon the segmental mechanism through the intermediation of the brain-stem. It is this last functional distinction rather than the first anatomical one, to which this study is dedicated. One limitation has been applied—the observations have concentrated on somatic motor activity, to the neglect of autonomic.

EXPERIMENTAL PROCEDURE.

To investigate the extrapyramidal motor and inhibitory activity of the cerebral cortex, two lines of experimentation have been followed: the one, to determine the variety of such activities within the cortex and to outline their fields; the other, to trace the projection downward from each field in a search for the subcortical mechanism upon which the cortex acts. The experiments have been performed on cats, and under ether anæsthesia except when decortication or decerebration rendered this unnecessary. For the fundamental procedure—severing the medullary pyramids—the basi-occiput was removed from the foramen magnum to high between the bullæ tympani, the dura slit, the basilar artery freed from the base of the brain, and a fine knife inserted down the median fissure to the estimated depth of the pyramids and turned laterally to cut first one, then the other of these clearly demarcated gross structures. Both cerebral hemispheres were widely exposed anteriorly, or one, from the olfactory bulb to the occipital pole. The medial surface of one hemisphere was uncovered by removing the greater part of the other and slitting the falx. The calvarium is best left intact over the dorsal surface of the hemisphere to be stimulated. The cortex in contact with the tentorium cerebelli was approached by gently retracting and raising the posterior pole of the hemisphere. Thus all the cortex except that buried in sulci and the olfactory parts has been made accessible to stimulation. Decortication and decerebration followed standard procedure. At the end of the experiments the animals were killed, the brains removed and hardened in formalin, and the sites of stimulation and gross extent of all lesions determined.

For stimulation, an apparatus designed by Myers (1936) was employed, delivering current in a 60 cycle sine wave over a range of 0·02 to 10 volts. Stimuli were either read directly in volts, or calculated as milliamperes after measurement of the inter-electrode resistance. As a routine, anal and stigmatic electrodes were employed, but each variety of observation has been confirmed by bi-polar stimulation, using paired or concentric electrodes. In general, the strength of the stimulus was either just slightly more than threshold, or maximal, and all data were collected in terms of strength of stimulus. But the figures have little absolute significance and will be largely omitted from the presentation.

The observations were made either in that stage of ether anæsthesia simulating the decerebrate state, in which the extensor or "anti-gravity" muscles are the seat of a steady tonic innervation, or in the lighter stage in which periods of strong tonic innervation of all the skeletal musculature alternate with periods of spontaneous activity. In the first condition the animals were usually placed back down (supine), with the extremities opposing gravity, in which position the action of gravity makes a striking demonstration of relaxation of tonic extension. In the second, the animals were supported on a stand with the legs dependent and free, and the head sometimes free, sometimes fixed. This arrangement allows gravity to demonstrate the relaxation of tonic flexion, and interferes least with the development and observation of motor activity. Decorticate and decerebrate animals were managed in a like manner, and anæsthesia was sometimes dispensed with and sometimes continued.

The cortical distribution of extrapyramidal activity has been examined in two groups of experiments. The first was designed to place extrapyramidal action in the pattern of total cortical function. Therefore the cortex was first explored with the pyramids intact, both for motor function and for inhibition dissociable from motor function by differences in threshold or in distribution. One or both pyramids were then cut, and the residual cortical activity re-examined over the lapse of hours. Twenty-two such experiments have been successfully carried through, four with unilateral, eighteen with bilateral pyramid sections. The lesions were variously placed, at the trapezoid level, at a low olivary level and by splitting the decussation, in an effort to determine whether or not leaving intact fibres passing from the pyramids to the reticular formation of the medulla and to the olives adds to the demonstrable cortical activity. No consistent differences were found. The completeness of the lesion was always verified by stimulating above and below the cut. This is essential when splitting the decussation because either the existence of uncrossed tracts, or the depth at which some of the fibres cross makes a functionally complete lesion attainable usually only with persistence. Bilateral pyramid section is a procedure entailing considerable shock and the second group of experiments was designed to minimize this. Therefore the pyramids were sectioned (two unilaterally, twelve bilaterally), and at periods of from three weeks to a year later the cortex was exposed and stimulated. These experiments added vigour and detail to the results obtained in the first series but otherwise confirmed them. The results of both series will be presented together to create the picture of cortical extrapyramidal action.

Investigation of the subcortical basis of cortical extrapyramidal action has required the employment of two types of experiment. The first attempted to determine the site of conduction through the medulla, having in mind the general relationships of the more important descending systems at that level. In ten animals, after the cortical activity had been thoroughly examined, the original pyramid section was extended on one side, first deep and then laterally, approximating finally to hemisection, and after each such extension the cortical activity was re-examined. The second attempted to trace, by direct stimulation of successively exposed parts, the descending cortical extrapyramidal activities through the cerebral white matter and into the brain-stem. The chronically prepared pyramid sections were utilized in this study, and a group of eight crucial bilateral pyramid sections was devoted entirely to it. In order to verify whether or not activity obtained in the brain-stem which resembles that from the cortex arises in descending cortical systems, or is intrinsic in the lower levels, these latter experiments were repeated on animals in which the descending systems from a part or from the whole of the frontal lobes were degenerate bilaterally. In two animals the peri-cruciate areas were radically excised dorsally and medially in order to remove Betz-cell cortex and the area frontalis agranularis, and in two others the entire frontal poles were resected from just behind the ansate fissure dorsally, to the base of the olfactory tract ventrally. Two months after operation in the first pair, and ten days in the second, the residual cortex was exposed and rapidly explored, and the brain-stem then thoroughly examined.

Although the procedure in this experimental study has been to examine, first, the total activity of the cortex, and then to extract from this the extrapyramidal action, the presentation of the results will reverse this order. The extrapyramidal activities will be described each in turn, as isolated phenomena. These will then be related, so far as possible, one to another and to corticospinal action. Finally, in summary, these elements will be reconstructed to form a tentative and certainly very incomplete picture of total function of the cerebral cortex at the level of projection on to the lower motor mechanism of brain-stem and cord. In evaluating the results of the experiments it should be borne in mind that the use of any anæsthetic whatever probably gives systems with few synapses an advantage over systems with many synapses which they may not possess in the normal state. A result obtained must represent in all cases the existence of a mechanism for action, but the results by no means necessarily indicate the relative efficacy of these mechanisms in normal function. In all probability the experiments demonstrate only the simpler components in the totality of function possible to the normal unanæsthetized animal.

EXTRAPYRAMIDAL INHIBITORY ACTION ON TONE.

Inhibition of tonic contraction in the skeletal musculature is the most easily demonstrated of all the extrapyramidal activities of the cat's cortex. This requires only the establishment of the very steady tonic extension of the pseudo-decerebrate stage of anæsthesia, or of the much less constant tonic innervation of the next lighter stage which flexion usually dominates. The demonstration then consists in the palpable relaxation of this tonic contraction, or preferably, with the animal in a suitable posture, by allowing gravity to pull the relaxing extremities down. The inhibition can be studied with the pyramids intact, when it is dissociable from motor action by a lower threshold or different localization, but it is much more easily and thoroughly examined after the pyramids are cut. The field for this action surrounds the cruciate fissure, as shown in fig. 1. Repeated examination of the entire surface (dorsal, medial and tentorial), of the parietal, occipital and temporal lobes, and of the remainder of the frontal lobe has yielded no trace of the action elsewhere. The gyrus proreus has received particular attention. And although the medial part of the precruciate gyrus at the base of the gyrus proreus exercises the inhibition most strongly, the gyrus proreus has itself been devoid of like action except in its posterior millimetre or two. Here, individual variation determines the result.

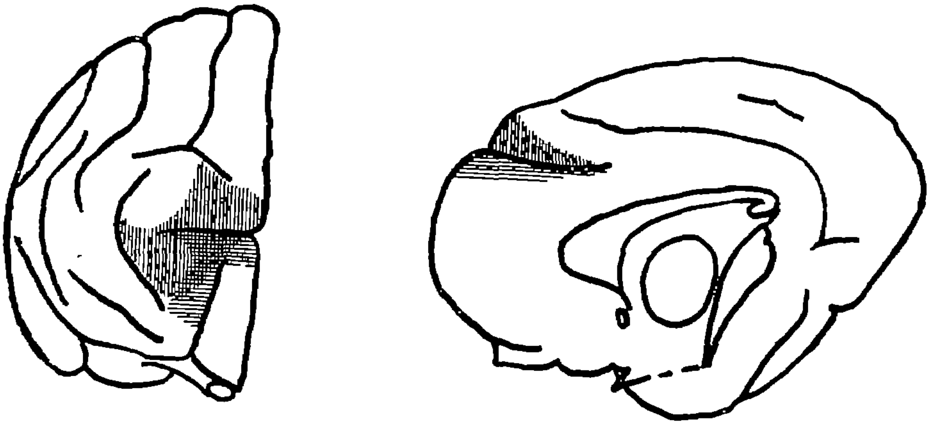

FIG. 1.—Area for relaxation of tonic contraction in skeletal musculature. Horizontal shading: anterior field. Vertical shading: posterior field.

When operating against a steady tonic extension, cortical inhibition of tone has exhibited certain general characteristics. To begin with, unless the tone is so weak that diminishing it at all allows the leg to collapse under its own weight, the inhibition operates—that is, the relaxation progresses—only during the application of the stimulus. Thus, repeated stimulation will cause an intermittent relaxation; continued stimulation, a steady relaxation. The strength of the stimulus, pitted against the strength of the tonic innervation, determines: first, the latency of the effect, sometimes a matter of seconds; second, its rate of progress; third, the completeness of the result; and fourth, its duration. Escape and post-inhibitory rebound are both common phenomena. Cortical inhibition interacts with excitation or inhibition of other origins in conventional patterns. Nociceptive stimulation (e.g. a pinch applied to the foot) sums with cortical stimulation to relax tonic extension, whereas a positive supporting reaction operates contrarily. Finally, when inhibition is brought into play together with pyramidal or extrapyramidal motor action, the timing of the two is such as to create the impression that posture is being abolished preparatory to movement. And not infrequently the tonic contraction abolished is in muscles subsequently innervated in the movement.

The posterior field for inhibitory action on tone.—Two varieties of inhibitory action on tone have been discriminated within the pericruciate area, in the two partially overlapping, partially discrete fields of fig. 1. The posterior field, vertically shaded, is virtually co-extensive with the motor area as ordinarily conceived, and with the distribution of giant pyramids in the cat's cortex as given by Langworthy (1927). It occupies the dorsal and medial post-cruciate gyrus with the exception of the part lateral to the end of the fissure, and the lateral part of the dorsal portion of the pre-cruciate gyrus. This field relaxes tonic contraction in conformity with the accepted pattern of corticospinal motor action, that is, in the proper extremity of the opposite side, and is effective against both tonic flexion and tonic extension. After recovery from the shock of pyramid section, and in very light anæsthesia, this inhibition is integrated with the more slowly recovering extrapyramidal motor function of the part, although the motor activity often requires somewhat stronger stimulation. But even so, if anæsthesia is pushed to the pseudo-decerebrate stage and extrapyramidal motor activity suppressed, the inhibition may usually be obtained alone. The inhibition is vigorous and of low threshold (0·02 to 0·2 milliamperes) if the pyramids have been cut weeks or months previously. But both the inhibition and the motor action with which it is associated recover slowly in the hours following pyramid section. This behaviour and the striking conformity of the field with Betz-cell distribution together suggest that these activities may represent collateral action from the corticospinal neurones above the level of section.

The anterior field for inhibitory action on tone, horizontally shaded in fig. 1, occupies the medial half of the dorsal part of the pre-cruciate gyrus and extends forward, lateral to the pre-sylvian sulcus as far as the anterior end of the coronal sulcus, while on the medial surface it follows the cruciate fissure to the end in a narrowing strip. Half-way down on the medial surface this strip has varied in width in different cats from 0 to 3 mm. On the dorsal surface variation has restricted the field in one animal to the posterior half of the pre-cruciate gyrus, while in others it has penetrated well forward into the gyrus proreus. In at least three animals (out of thirty-six) the field has reappeared unmistakably posterior to the cruciate fissure, once on the whole medial surface, and twice on the dorsal surface close to the midline. Rioch and Rosenblueth's (1935) fundamental study of the activity in question also seems to exemplify such variability. The anterior inhibitory field thus invades the Betz-cell territory laterally, in the pre-cruciate gyrus, and probably also in the depth of the fissure, but it concentrates in the cortex anterior of this. Where Langworthy has studied this cortex, he considers it to be area frontalis agranularis, but the medial and anterior prolongations of the field have not been examined microscopically. Whether or not the field is laid down in a cortex of characteristic cyto-architecture from end to end, is, therefore, unknown.

The anterior tone inhibiting field has one outstanding action: it relaxes tonic extension of the decerebrate type in the ipsilateral extremities, and in the head, trunk and tail. All parts of the field operate alike in this, with no subdivision corresponding to parts of the body. The fore-leg is the part usually most strongly affected, and may be the only part acted upon. Contralateral action may accompany the ipsilateral action, but not from all parts of the field alike. Thus the medial surface has acted contralaterally only once, on the crossed hind-leg. But on the dorsal surface, in the area of overlap of the anterior and posterior fields, both fore-legs are frequently relaxed together, often together with either or both hind. This almost certainly represents conjoint excitation of the two fields because as the posterior field becomes ineffective during the course of a long experiment, the effect of the anterior field becomes increasingly and finally entirely ipsilateral. In final analysis, a certain generality of action may have to be accorded the anterior field, but ipsilateral action certainly characterizes it. In the anterior field threshold tends always to be high, often double that of the posterior field when both are simultaneously effective. The field is little affected by the shock of pyramid section, and is so exceedingly resistant to fatigue and exhaustion, and to anæsthesia, that for hour after hour of repeated cortical stimulation its powerful inhibitory action may remain substantially undiminished, while all other extrapyramidal action weakens and disappears. Only corticospinal action, when one pyramid remains intact, is more viable.

Proof is lacking that two distinct mechanisms are represented in the two fields of inhibitory action thus discriminated, although the differences in cortical localization and in side of action in the periphery, in susceptibility to shock and to exhaustion indicate that it may be so. In any case, the two varieties of inhibitory action on tonic contraction ultimately meet, for ipsilateral action from one hemisphere may be made to facilitate, or to supplement, contralateral action of the other hemisphere and the reverse. Thus, when maximal stimulation of one field has incompletely relaxed a tonically extended extremity, shifting rapidly to the other field of the opposite side may complete the relaxation. And threshold stimulation of the posterior field may substantially reduce the usually much higher threshold of the opposite anterior field, if the second stimulation follows directly on the first. Such inter-action has been more clear-cut for the fore-legs than for the hind.

EXTRAPYRAMIDAL INHIBITION OF MOVEMENT.

The cat's cerebral cortex contains two inhibitory fields powerfully effective against movement, one frontal, the other in the sylvian region. Except that the frontal field is the stronger, the two have shown a like action. This may be characterized as arrest of movement—a positive phenomenon—in contradistinction to mere cessation. A third, and weaker, field is present on the tentorial surface of the occipital lobe and is continuous, on the one hand through the gyrus fornicatus with the frontal field, and on the other hand with the sylvian field lateral to the rhinal fissure. These parts exert a quieting influence on spontaneous movement. Fig. 2 shows the total field for inhibitory action on movement in its two degrees of effectiveness.

The frontal field consists of the gyrus proreus in its entirety, dorsal, lateral and medial, the adjacent ill-defined gyrus genualis, and the anterior part certainly of the gyrus fornicatus (terminology after Winkler and Potter). Posteriorly it overlaps the anterior tone inhibiting field, whereas laterally the presylvian sulcus makes a sharp boundary. Cyto-architecturally this cortex is all much alike—thin and poorly differentiated. Langworthy (1928) describes the dorsal gyrus proreus which he examined as retaining throughout life an embryonic appearance. Campbell (1905) says of his prefrontal area "the cell lamination is uninteresting," and emphasizes the poverty in cells and fibres both of this area and of the limbic area. In both the internal pyramidal layer is that best developed.

The lateral field is by no means so clearly delimited. The action is strongest, certainly, in the anterior sylvian gyrus, but demonstrable always in the posterior sylvian gyrus as well. And from here the field has extended forward, upward and backward into the ectosylvian gyri, to a variable extent in different animals. Indeed, traces of the action have been obtained across the suprasylvian sulcus, in the suprasylvian gyrus, and in such cases the field has occupied all the territory between the anterior motor area on the one hand and the posterior motor area on the other. Evidently the activity is either very widely distributed in the cortex or provided with unusual facilities for trans-cortical conduction. Whether large or small, however, the lateral field exists independently of the more strongly acting frontal field, for its action was quite undiminished when examined in two cats ten days after radical resection of both frontal poles. Cyto-architecturally, the lateral field is much better differentiated than the similarly acting frontal field, and has a very much richer fibre supply, but it shows in common with this latter the characteristic that the internal pyramidal layer is the layer best represented.

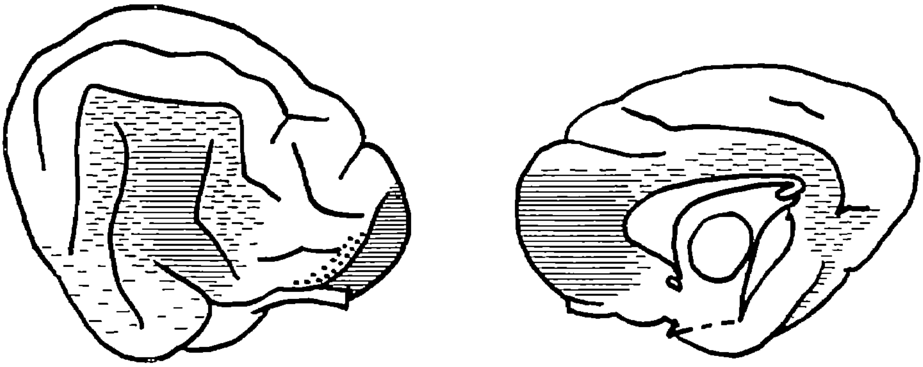

FIG. 2.—Area for inhibition of movement, horizontally shaded. Solid shading: arrest. Broken shading: quieting. Stipple: field for licking and chewing.

The occipital field has been difficult to define exactly because of its deep position on the tentorial surface. The field begins where the occipital motor field leaves off, occupying the cortex lateral to the rhinal fissure, and continuing back into the gyrus postsplenialis, and through this into the gyrus fornicatus. The upper part of the field may invade Campbell's area striata, but it lies predominantly in his extrarhinic and limbic areas. Of these two the extrarhinic area is the better developed, but both contain deep and unbroken internal pyramidal layers.

The inhibitory action of these fields has been examined against a variety of activities deliberately excited or spontaneously occurring. Rhythmic activities with rates which may be stated in times per minute before, during and after inhibitory stimulation lend themselves best to the study. Respiration is an outstanding example of the sort, with the advantage that it is always present, but in a light stage of ether anæsthesia the cat develops others—side-to-side movements of the tail, striking, pawing, or placing movements of the fore-legs, diagonal progression, and nystagmoid or oscillating movements of the eyes. And if these do not present spontaneously, they may frequently be excited from the cortical motor areas with after-discharge sufficient to serve the examination. All these movements presenting singly or in combination, and many other random movements besides, have been slowed or stopped by stimulating in one or the other of the fields outlined, and the evidence has been considered conclusive when a performance which had been repeating regularly for perhaps one to ten minutes slowed or stopped during stimulation, and resumed again thereafter. Threshold tends to be high, 1 to 2 volts under good conditions, although some effect has been obtained with half a volt (0·2 ma.), but with an adequate stimulus the inhibition acts rapidly. The demonstration is striking in proportion to the vigour of the activity to be inhibited. Thus running or alternate striking movements of the fore-legs may be brought to an abrupt halt—eyes front, head raised, back and tail straight, legs extended or semi-flexed, and held thus for perhaps a minute. And this assumption of an attitude gives to the action of these fields when at a maximum a characteristic appearance of fixation at attention. At a minimum the effect appears to be merely one of quieting the animal, when head, tail, and extremities all droop. Respiration may show this quieting influence almost to the stage of surgical anæsthesia.

On respiration, the effect takes various courses. Breathing may become rapid and shallow and then cease, or slow and full, or slow and shallow, and then cease; or it may cease abruptly; or, most commonly, it merely slows but does not stop at all. On continued stimulation in the frontal field respiration has been held in arrest for a maximum of twenty-eight seconds, but usually it escapes much sooner. Respiration may resume either in a rapid shallow rhythm, or forcibly, in a gasp. If the inhibitory stimulation is removed while inhibition is still effective, forcible resumption at increased rate and depth is the rule—a form of post-inhibitory rebound. The frontal field far exceeds the lateral field in the strength and certainty of effect on respiration.

Against patterns of movement in the extremities and tail the frontal and sylvian fields are almost equally effective. Inhibition may be transitory or permanent. The activity may escape from inhibition; or resume on release from inhibition with increased rate and vigour; or recover only slowly during many seconds; or not resume at all. In general, the more vigorous the performance, the less enduring the inhibition, and the more certain the resumption in rebound. Running, for instance, is rarely held in suspense long, whereas leisurely side-to-side movements of the tail which have been repeating once in two to three seconds for half an hour or more, may be suspended indefinitely. Movements which are the after-discharge of cortical stimulation are easily stopped but never resume at all. When cortical stimulation slows, but does not arrest a movement, rate and amplitude may, as in the case of respiration, be differently affected. Thus movements of the eye-ball tend to become rapid and of smaller amplitude, whereas rate and scope usually diminish together in movements of the extremities and tail.

The Vogts' observation on monkeys (1919), that rhythmic mastication excited from their field 6bβ, could be "denervated" or inhibited by stimulating forward in their area 8γ, or further forward still, has been duplicated in the cat. Rhythmic chewing and licking may be set in train by stimulating lateral to the presylvian sulcus (fig. 2), and then brought to a halt by shifting the electrode across the sulcus to the gyrus proreus. But such movements cannot be started medial, nor stopped lateral to this sulcus. They have also been stopped from the sylvian field, but the action of the occipital field in this respect has not been examined.

The action of these fields is primarily on movement—movement of any variety, random or rhythmic. Against tonic contraction in the musculature they are ineffective. Postures which either precede, or are the immediate remainder of, movement may be abolished, but a steady tonic innervation such as the extension of the pseudo-decerebrate state is quite unaffected. Indeed, the orientation to the front which accompanies action of these fields at a maximum involves strong tonic innervation, either as tonic extension or as tonic innervation of all the musculature producing semi-flexion, and suggests a reversion of control to the tone producing mechanism when movement is arrested. Thus these fields appear to operate—not to stop activity in muscle—but to stop the processes leading to motor discharge in patterns of movement.

Although the action of these fields has been described as though it represented a unit mechanism, this is by no means certain. A distinction should, perhaps, be made between action on respiration and action on the complexly patterned movements of the extremities. In the frontal field the latter effect has been restricted to the gyrus proreus, whereas inhibition of respiration has been obtained several times from the pre-cruciate gyrus out to the lateral end of the cruciate fissure, in territory yielding at the same time motor activity in the extremities. A more important distinction should probably be made between "fixation at attention" and the "quieting effect." In that case, the former belongs to the gyrus proreus and the anterior sylvian gyrus, and makes the action of these parts outstanding. The latter is, then, the widespread action—so widespread that even the motor fields have seemed to possess it when by chance their motor functions were in abeyance. In fact the only cortex which has not at some time yielded this quieting influence has been that part of the striate area along the crest and on the medial surface of the hemisphere, in the post-lateral, suprasplenial and splenial gyri.

EXTRAPYRAMIDAL MOTOR ACTIVITY.

The motor activity obtained from the cat's cerebral cortex after both pyramids are cut, differs fundamentally from the simple phasic result of corticospinal stimulation obtained either from the cortex in so-called surgical anæsthesia, or from the distal end of a cut pyramid in any state. This latter and unquestionably corticospinal action is a simple crossed movement, usually of flexion, but sometimes, especially in the decerebrate animal, of extension. It appears without delay, is sustained for the duration of the stimulation if this be not too long, and shows no progressive elaboration and no appreciable after-discharge. In the pyramids hind-leg action has a lower threshold than fore-leg action, probably because the hind-leg fibres lie superficially and those to the fore-leg deeper (McKibben and Wheelis, 1932). Distal limb-segments usually have a lower threshold than proximal. Pitted against an active tonic extension in the extremities, stimulation of the pyramids will abolish this in favour of active flexion, and threshold stimulation may break tonus into clonus without producing flexion. But relaxation is not obtained from the pyramids unaccompanied by motor action, as it is from the cortex. Therefore, although reciprocal inhibition must almost certainly enter into corticospinal action as a property of the segmental mechanism upon which the corticospinal system must act, no independent inhibitory action can at present be ascribed to the system. It is a motor system of the simplest sort.

In contrast with the simplicity and predictability of corticospinal action, extrapyramidal motor action is complex and unpredictable. It begins to show first in a light pseudo-decerebrate stage of anæsthesia, and augments in complexity and variety with each lighter stage. It is extremely susceptible to shock and to interference with cerebral circulation, and appears commonly in fragmentary fashion only. But even these fragments are complex synergic movements, and the fully developed movements may become well integrated and significant acts. In further contrast with corticospinal action, the extrapyramidal motor response is slow to appear, builds up slowly and tends to outlast the stimulation as rhythmically repeating movement for seconds, or as posture—sometimes indefinitely. Respiration accelerates and the tail becomes active whenever any extrapyramidal motor activity reaches a certain intensity, without giving evidence of more specific localization.

Cortical extrapyramidal action gives rise to a bewildering variety and complexity of effects of which only the more characteristic and constantly recurring can be described. Differences in surface localization of the different activities have yielded insight into the total of one sort, and differential anæsthetization, of another sort. Just as in the intact animal, corticospinal function may almost certainly be freed of all recognized extrapyramidal function by pushing anæsthesia to the point of muscular relaxation, so, too, with the pyramids cut, a basic group of extrapyramidal motor reactions may be dissociated from the acts into which they are incorporated by, as it were, decorticating or decerebrating the animal with ether. By such analysis, the extrapyramidal motor activities, with one exception, have appeared to be organized in stages, possibly representing successively higher levels of projection into the brain-stem. First to emerge with lightening anæsthesia is a stereotyped synergic movement in a crossed extremity, of no more discoverable teleological significance than pertains to corticospinal movement. This is sustained for a brief time, and then in spite of continued stimulation, relaxes. With lighter anæsthesia, however, this primary movement may terminate, not in relaxation, but in a second movement, almost its opposite, the whole constituting a sequence whose utility begins to be apparent. The other extremities and the body musculature will now be tonically innervated in an appropriate pattern. With somewhat lighter anæsthesia this sequence may begin, first to repeat in the one extremity, and then to alternate between two homologous or contralateral extremities until finally the whole performance emerges. And with lighter anæsthesia still, the same performance frequently becomes spontaneous. Extrapyramidal motor activity has been obtained from four areas on the surface of the cat's cortex, one frontal, a second almost contiguous with this, lateral, a third, parietal, and a fourth, far removed on the occipital pole.

The frontal extrapyramidal motor area presents three fields of action, which will be designated, from their location, anterior, medial, and posterior. They are shown in fig. 3. Two of these fields yield a primary movement of characteristic form, which may be elaborated into a performance of unmistakable purposive and emotional significance, whereas the third has yielded a simple movement only. All three fields overlap in the precruciate gyrus, and are to be considered—not as subdivisions of the cortical area—but as functional units. Two of the fields are homogeneous throughout, all parts yielding the same activity, though not with equal intensity. The remaining field is subdivided into fore- and hind-leg territory. When any two of these fields are active in the same animal at the same time, they may be brought into competition for the final motor mechanism in the region of overlap with results which support the concept of their independence.

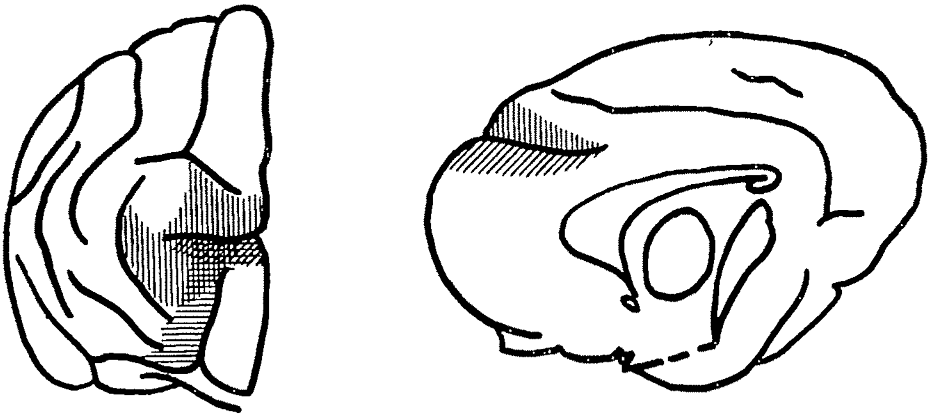

FIG. 3.—Frontal extrapyramidal motor area. Horizontal shading: anterior field. Vertical shading: posterior field. Diagonal shading: medial field.

The posterior extrapyramidal motor field is co-extensive with the posterior tone-inhibiting field, the two forming an integrated whole. Together, they also appear to be co-extensive with the area of distribution of giant pyramids in the cortex (Langworthy, 1927). Certainly they show the subdivision into fore- and hind-leg territory ascribed to that field. The hind-leg territory stretches from end to end of the cruciate fissure, lying behind it. The fore-leg territory takes in the lateral two-thirds of the pre-cruciate gyrus and the lateral corner of the post. Both avoid Langworthy's area D, which is consistent with his description of this cortex as cyto-architecturally a sensory projection area, and not motor.

The primary movement obtained from this large field is usually a flexor synergy in the proper crossed extremity, from which, with lightening anæsthesia, either diagonal progression or a performance to be called "the pleasure reaction" may develop. The flexion appears first at wrist, or ankle, and digits, and may be limited to these if the stimulus is minimal or the animal poorly excitable. Otherwise it recruits in turn, elbow and shoulder, or knee and hip, and brings the extremity up under the body in tight flexion, thrusting hip or shoulder high above the back. The claws are extruded and rolled into the tightly balled paw. Sometimes flexion is preceded briefly by extension at wrist and digits, especially if the leg is already in tonic flexion. And abduction of the fifth digit has often been dissociated as the lowest threshold element in this preponderantly flexor reaction. On continued stimulation, the flexion and retraction may be maintained for perhaps half a minute, after which they either relax or proceed to reverse. Reversal undoes the original sequence in direction and in order, and in the same leisurely tempo which characterized the original. Thus flexion at all joints from the distal to the proximal ending in retraction, is succeeded by protraction and by extension at all joints from the proximal to the distal, ending in fanning of the toes. The claws are extruded throughout. At this stage, if not before, the ipsilateral homologous extremity is usually tonically extended. The primary movement and the reverse movement constitute a cycle which may repeat rhythmically, on continued stimulation, almost indefinitely. The rhythmic process may involve less than the total extremity, in which case the omitted segments are always proximal. The next phase of development produces alternate action between two or more extremities, and differs somewhat according to the performance emerging.

In the development of progression rhythmic action usually accelerates until all the joints are involved in rapid sequence or together, and the ipsilateral homologous extremity and the remaining extremity of the contralateral side are tonically extended and retracted. Alternation may begin either between two homologous extremities or between the two contralateral extremities, but usually these three are quickly brought in, and the fourth tardily. As progression gets under way flexor and extensor phases of the pattern follow in unaccented rhythm unless superimposed on a background of strong tonic extension. Then a beat may become apparent, the flexor phase being slow, the extensor, fast in a thrust. Very occasionally, if the hind-leg portion of the field is less excitable then the fore, or after a period of stimulation of the fore, stimulation in the hind-leg territory has initiated progression in the crossed fore-leg, but usually the distinction between the two parts of the field is clear-cut, and each starts progression in the proper crossed extremity.

"The pleasure reaction" involves primarily only the fore-leg, and is obtained only in fore-leg territory if facilitation is avoided. It is characterized even as a primary movement in the crossed fore-leg by great deliberateness. The ipsilateral fore-leg is first tonically extended, and then commences the deliberate sequence, but exactly out of phase with the original. The hind-legs may be tonically extended or semi-flexed, but do not otherwise participate. As soon as the fore-legs commence alternate action, the total activity is unmistakably one of the commonest performances of the intact animal, used by kittens in nursing, and retained by adult cats as a concomitant of pleasurable excitement.

The deliberateness of this "pleasure reaction" has permitted careful examination of the conditions under which it operates in a manner not possible with other more violent extrapyramidal motor performances. To begin with, the pyramids being cut, all parts of the field produce the same movement at any given time, except where competing fields overlap, but threshold and intensity of action may not be the same throughout. The lowest threshold, most strongly acting part lies just anterior and lateral to the lateral end of the cruciate fissure. Although the primary synergic movement appears always in the crossed fore extremity, when the stage of alternation is reached, action started from a point in one field may be kept up by stimulating any point in that or the opposite field without interrupting the sequence. Moreover, when stimulation is discontinued, for a brief time after activity has ceased, renewed stimulation either at the original point or at any other point in the same field of either cortex may cause the sequence to resume where it left off and to continue, without respect to the side stimulated. But if the interval has been too long, it starts again in the proper crossed extremity. Finally, in the light anæsthesia essential to the complete performance, passive flexion of the extended paw, or extension of the flexed paw may act as does cortical stimulation to excite and sustain the integrated sequence. And in just lighter anæsthesia the act becomes spontaneous.

The posterior extrapyramidal motor field has also yielded a second primary movement, of extension and retraction, activating from fore-leg territory the crossed fore-leg, and from hind-leg territory the crossed or both hind-legs. Stimulating a newly.exposed field, or after an interval of rest, is particularly prone to yield such extension, which is replaced by flexion on repeated stimulation. This primary movement has never developed further.

Progression and the pleasure reaction have been the only two recognizable acts obtained from the posterior extrapyramidal motor field. Under the conditions of experiment, as in the intact animal, they have been mutually exclusive. When progression presents, it is elicitable from the entire field. When the pleasure reaction presents from fore-leg territory, the hind-leg territory has been without action. The virtual identity of the synergic movements primary to the two suggest that basically they depend upon the same subcortical projection, but how the difference enters then presents a problem.

The anterior extrapyramidal motor field is not confined by recognized cyto-architectural divisions of the motor area. It occupies the medial half of the pre-cruciate gyrus and extends forward lateral to the presylvian sulcus to expand over the anterolateral surface of the brain. The lowest threshold, most consistently active part of this field lies just lateral to the posterior end of the presylvian sulcus, where, perhaps, this field has the benefit of some summation of action with the posterior field. However, the portions of the field stretching forward across the coronal and orbital gyri have been effective two months after radical removal of the entire peri-cruciate region so that the field outlined in fig. 3 represents projected action, and not transcortical conduction to a low threshold pre-cruciate part. With the peri-cruciate cortex in situ, the field usually acts primarily on the crossed fore-leg, producing, simultaneously, protraction at the shoulder with or without abduction, half flexion at the elbow with pronation or supination, extension at the wrist, and extension, followed almost at once by flexion of the digits. The claws are usually extruded. Thus the paw is brought up beside the face or over the head in a non-sequential movement. However, when the peri-cruciate region has been removed, leaving only the anterior part of the field, action has been primary in the crossed hind-leg almost as often as in the fore. The hind-leg is then brought up alongside the flank in a corresponding movement. This field usually becomes active only in quite light anæsthesia, and the primary movement rarely appears without the full performance following.

Alternation starts abruptly; the protracted and flexed leg breaks into extension and retraction, giving to the whole performance its outstanding characteristic—a beat. The ipsilateral fore-leg is extended, and may begin to alternate with the other. The hind-legs are extended or semiflexed, back humped. tail active, respiration accelerated. Finally, the animal may begin to run. The frontal adversive field lies partly within the field of this activity, and the performance is usually, but not always, accompanied by deviation of eyes, head and body away. When well developed, the movement repeats 15 to 30 times per minute. The activity of this field has presented several variants of different purposive and emotional qualities. Thus when the movement is executed swiftly, with the claws out, either in full pronation or in partial abduction, supination and adduction, it is best characterized as striking, or, after Ward and Clark (1936), as batting. This is its most common appearance. On the other hand, executed somewhat more deliberately, with claws often sheathed, the reaction has the appearance of placing. And it is, perhaps, significant that if pressure is brought to bear on the paw-pads by bringing the palm of the hand up beneath them, the reaction stops at once, unless the animal is excessively active, and is succeeded by a positive supporting reaction, whereas pressure similarly exerted during the course of the pleasure reaction has no such effect.

The progression obtained from this anterior motor field presents a problem; should it be differentiated from the progression obtained in the posterior field, or not? In the anterior field the onset tends to be precipitate, in the posterior field, deliberate, but the subcortical mechanism activated must be much the same in both cases. The anterior field does not necessarily operate through the posterior, for in the two animals in which the peri-cruciate cortex had been removed two months before, stimulation of that part of the anterior field remaining, precipitated running. Possibly diagonal progression is a unit mechanism distributed over both anterior and posterior fields, but variously modified in the two fields by other activities therein localized.

If this anterior field and the posterior field are simultaneously and about equally active, stimulation in the region of overlap produces a characteristic result. Usually the pattern of the posterior field dominates, and the tempo of the anterior. Thus the deliberate flexor synergy of the posterior field may be obtained with the tempo and beat of striking. A shift of a millimetre or two in either direction from the region of compromise throws the response completely one way or the other.

The medial extrapyramidal motor field has been the most difficult of all the extrapyramidal motor fields to study. It becomes excitable only under the very best experimental conditions, and in exceedingly light anæsthesia. Its dorsal extent is overlapped, and usually obscured, by the anterior field, and only the chance inexcitability of the anterior field together with the frontal adversive mechanism in three animals, has exposed the medial field to thorough examination. However, the presence of a primarily ipsilateral motor effect from the dorso-medial part of the pre-cruciate gyrus was early recognized, and gradually evidence has accumulated sufficient to define the field and characterize its action.

The medial extrapyramidal motor field lies just anterior to the cruciate sulcus from end to end, as shown in fig. 3, and is restricted to the pre-cruciate gyrus. Although this field has not extended forward lateral to the sulcus presylvius with the ipsilateral tone inhibiting field, its activity none the less complements that of the inhibitory field remarkably, except for an enormous discrepancy in excitability of the two. But just this difference in excitability may restrict the extent of the motor field demonstrable, in which case motor and inhibitory action may have the same relationship here as in the posterior field. The field produces, ipsilaterally, a steady tonic flexion, adduction and supination of the fore-leg, with or without flexion and adduction of the hind. The claws are out. Contralaterally, the extremities may be tonically extended, retracted and abducted, especially from the medial surface where there is no conflict with other primarily contralateral fields. Or they may be flexed, one or both. Usually the tail is deviated and the trunk ventrally flexed and concave to the side stimulated. And if the frontal adversive field, which borders the field in question anteriorly, is, by chance, inactive, the head is also bent to the side stimulated. On continued stimulation the tonic innervation is steadily maintained, often for half a minute or more, but it has never shown any tendency to reverse or to develop further. Stimulating in the region of overlap of this medial field with the lateral field makes a striking demonstration of the difference in the flexor synergies of the two, for the crossed fore-leg comes up under the body in pronation, the ipsilateral across the chest in supination.

The lateral extrapyramidal motor area is curiously small and isolated, lying in the inferior part of the anterior ectosylvian gyrus as shown in fig. 4. It is not very often active, but in such animals as have exhibited it, the field has been sharply outlined and threshold fairly low. The activity is exceedingly susceptible to the shock of acute bilateral pyramid section and to very moderate loss of blood, indicating, probably, that the subcortical projection is small in volume. On the other hand, it is large in scope, for this small area has reproduced all but one of the complex activities made familiar in the frontal area, and for this reason has been accorded the status of an independent area.

The field yields as its most common response the pattern of synergic flexion in the crossed fore-leg which brings that leg up under the body in pronation with the claws out. The movement then reverses and becomes rhythmic in the one leg, but has only once gone on to alternate between the two fore-legs, in this instance in the unmistakable pattern of the pleasure reaction. Both hind-legs were then retracted and semi-extended. Later on this same field produced excellent movements of placing in the crossed fore-leg, repeating these on repeated stimulation. In this animal the peri-cruciate cortex had been removed, but the pyramids were intact. In two of the series of chronic bilateral pyramid sections the response from this lateral area was primarily ipsilateral, producing flexion and supination of the fore-leg with the claws out, with head, body and tail concave to the side stimulated. The contralateral fore-leg was in one case extended and abducted, and in the other flexed. On one occasion the crossed fore-leg executed vigorous striking motions,

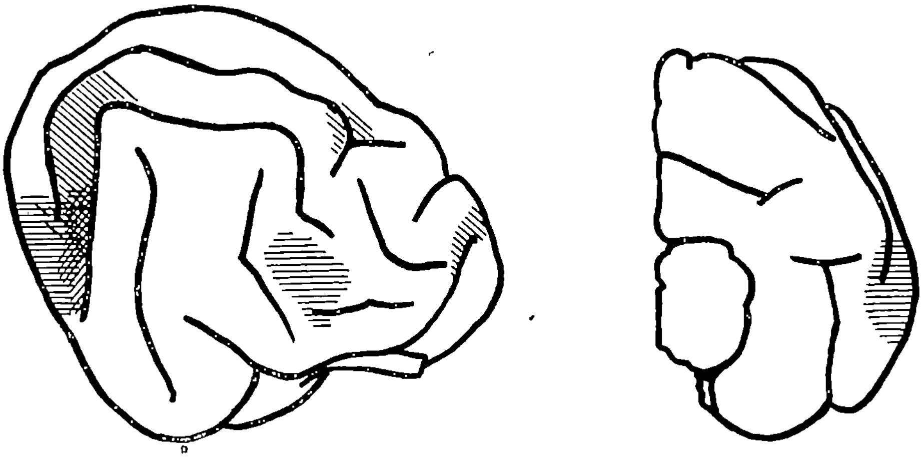

FIG. 4.—Lateral and posterior extrapyramidal motor areas; horizontally shaded. Adversive fields: diagonally shaded.

while the ipsilateral fore-leg was flexed across the chest. The field has had an uncommonly strong accelerating action on respiration, twice without other visible effect. And the tail is set into motion or accelerated in spontaneous motion readily. Only progression has been wanting to complete the total effect of cortical extrapyramidal action. Because of the manner in which this lateral area reproduces the activities of the frontal fields, continuity between the two has been persistently sought, but the lateral area has always seemed detached, although a variety of activities utilizing the cranial nerves may fill the gap. This small and infrequently active lateral area appears, therefore, to constitute a discrete field for cortical extrapyramidal action, but the significance of an extrapyramidal motor area in the site remains obscure.

The posterior extrapyramidal motor area of the cat's cortex probably represents a conjunction of the occipital and temporal motor fields of primates. It occupies the posterior part of the gyrus suprasylvius medius and the whole gyrus suprasylvius posterior, passing thence on to the tentorial surface. The field is shown in fig. 4. It lies between the sensory receptive field for sight above and that for hearing below if this latter is localized low in the gyrus ectosylvius posterior as is generally believed. Primarily this is a field for orientation, with adversion of the eyes as the usual threshold reaction in the upper part, and pricking of both ears below. Other variants such as upward or downward movements of the eyes are also obtained, and other movements in the facial musculature such as closure of the eyes and ipsilateral whisker movements. Barris (1936), has located a pupillo-constrictor centre within it. Action on extrinsic or intrinsic ocular musculature or on facial musculature has no place in the present study, although head adversion comes within its scope. But the movements of the extremities which this cortex yields occasionally, and the radiations beneath fairly consistently, are typical examples of extrapyramidal motor action.

This posterior motor area, like the lateral area, is effective only under the best experimental conditions, and rarely comes through acute bilateral pyramid section in an active state. This is true to a lesser degree even of the adversive activity of eyes and ears. After chronic bilateral pyramid section the field acts substantially as it does with the pyramids intact. The field has reproduced, at one time or another, all the actions described from the frontal area, although whole acts tend to appear rather than the primary movements. Striking or placement of the crossed fore-leg is the most frequent of these responses, with diagonal progression second. Both patterns of synergic flexion, in pronation and in supination, have developed ipsilaterally. On one occasion ipsilateral flexion in pronation proceeded, first to reverse in the one fore-leg, and then to alternate between the fore-legs, in a curiously violent version of the pleasure reaction. The field has had the usual accelerating effect on respiration and on spontaneous movement of the tail, even in the absence of all other visible action from the field, including adversion. Within the posterior motor area action on the extremities is stronger posteriorly, along the posterior edge of the hemisphere, whereas adversion is stronger in the gyrus suprasylvius medius and the upper part of the gyrus suprasylvius posterior, indicating some degree of specialization within the area. But the several patterns of response in the extremities do not concentrate separately, as is the case in the frontal area. This posterior extrapyramidal motor area appears, therefore, like the lateral area, to be a compound field, capable of producing from all parts alike the full range of recognized extrapyramidal motor action. But here the obvious association with the adjacent sensory receptive fields for sight and probably for hearing lends significance to the location of a motor area in the site.

The parietal extrapyramidal motor area is also a small area, lying just behind the ansate fissure (fig. 4). It is primarily an adversive field, but not on a par with either the frontal or the occipital adversive fields. It is unstable and unpredictable. Most frequently it rotates the head on the long axis to face away from the stimulation, but it has also deviated the eyes up, down and away. Occasionally it accelerates respiration, and once the crossed fore-leg executed an unmistakable movement of placing. This field is in continuity both with the hind-leg area and with the ear field of the coronal and suprasylvian gyri, and may, perhaps, be an integral part of the total frontal motor area. But it is also reminiscent of the parietal motor fields located by the Vogts (1919) and by Foerster (1931) along the crest of the hemisphere in monkeys and in man.

This concludes the description of cortical extrapyramidal action presented from the point of view of the most complete performance obtainable in a well-defined field. For motor activity, however, the complete performance is the exception rather than the rule. Thus the pleasure reaction has presented in its entirety in only eight animals out of forty; about half the series have yielded diagonal progression; about three-fourths, striking or placing activity, while ipsilateral action has developed into a significant performance only once. The inhibitory activities have been more reliable. The anterior tone inhibiting field has been fully active in all but two animals; the posterior, excitable to some degree in almost all. And after the inhibitory action on movement was recognized and routinely investigated, this never failed to be demonstrable, at least against respiration if no other recurring activity was available for the study. No single animal has ever presented the totality of the cortical extrapyramidal activity described, and the factors which determine what shall appear and what shall not, are largely obscure. It is, however, a fair assumption that they derive from unfavourable experimental conditions, and that the sum total of cortical extrapyramidal action put together from all the experiments, represents certainly no more, and probably very much less, than the possibilities for cortical extrapyramidal action possessed by every intact cat.

THE SUBCORTICAL BASIS OF CORTICAL EXTRAPYRAMIDAL ACTION.

Each of the extrapyramidal activities located in the cat's cerebral cortex represents direct projection on to the subcortical mechanism, for each has been obtained equally well, and usually more strongly, from the white matter beneath its cortical field and from the internal capsule. The concentration of fibres from a large area of cortex into small compass in the radiations probably underlies the stronger action of these parts. Starting from the cortex, the extrapyramidal activities have been traced by electrical stimulation in the decorticate preparation, through the cerebral white matter and into the internal capsule where they are spread out in orderly array. Shelling out the head and body of the caudate nucleus to expose the capsular arrangement makes no noticeable subtraction from the total. Their further course has been sought by stimulating the cut surface of successively more posterior transections of the brain-stem, but in the transition from mid-brain to thalamus the activities largely disappear from the pes pedunculi, and similar activities picked up in other parts prove to be intrinsic in the brain-stem.

Inhibitory action on tone may be brought to bear in full force on tonic extension in the ipsilateral extremities from the anterior limb of the internal capsule, but below this nothing comparable in clarity and strength with the cortical action has been demonstrable. Stimulation of the pes pedunculi has usually been without any inhibitory action, although occasionally it has had a transitory effect. Then tonic extension was relaxed ipsilaterally from the most mesial part, and perhaps bilaterally over a larger extent. Crucially prepared and chronically prepared pyramid sections have been alike in this uncertainty of action. Inhibitory action on tonic contraction has been sought from the ventricular surfaces of the caudate nucleus, thalamus and hypothalamus, and from the tectum of the mid-brain without result, but the tegmentum may yield it. This happens when hæmorrhage or exhaustion has rendered motor activity inexcitable or raised its threshold. If motor activity is deliberately suppressed by careful anæsthetization while steady tonic extension is conserved, a powerful inhibitory action on the tonic extension is freed from the motor "tegmental reaction" with which it is ordinarily integrated, and becomes readily demonstrable. The dissociated inhibition, like the tegmental motor reaction, has an exceedingly low threshold, often less than 0·1 volt. The effect is predominantly ipsilateral and on the fore-leg. It is abrupt and enduring such that decerebrate rigidity, which is, as it were, wiped out, may require half a minute or more to recover. Thus it reproduces, only more strongly and at lower threshold, the inhibitory action on tone of the anterior cortical field. But the action persists in full force when the systems descending from this cortex, and indeed, from the entire frontal lobe are degenerated, and depends, therefore, upon structure intrinsic in the brain-stem. Whether or not this brain-stem mechanism serves cortical inhibition as a relay, is beyond determination from the evidence at hand.

Inhibitory action on movement has been followed from the frontal region of the brain into the anterior limb of the internal capsule, and from the occipital and sylvian regions into the lateral end of the forming crus cerebri between the thalamus above and medially and the lentiform complex below. Transecting the brain-stem behind the thalamus abolishes the sustained rhythmic activities on which its demonstration depends, and thus prevents further pursuit, except of the effect on respiration. Like action, except for the effect on respiration, has sometimes been obtained weakly from the head of the caudate nucleus, and strongly from the lentiform complex, especially from the outer segment of the globus pallidus, and with stimuli too weak to excite the motor or tone inhibiting systems descending through the internal capsule. Since one of the terminals of subcortical projection from the regions in question is the striatum, three possibilities may underlie this result. The stimulating current may spread to excite a system descending the capsule. Or such a descending system may be excited antidromically, through collaterals into the striatum. Or a proper striate action may here be in evidence. Inhibitory action on respiration has twice been obtained from the medial tip of the pes pedunculi, and in both instances all the cortex yielding this action was in place.

The extrapyramidal motor activities are disposed around the head of the caudate nucleus, at the junction of corona radiata and capsule, in the following order: Ipsilateral fore-leg flexion medially; striking or placing and adversion at the anterior end; contralateral fore-leg flexion followed by contralateral hind-leg flexion on the anterolateral border, and after an interval, at the juncture of body and tail, adversion again, with striking or placement, or the ipsilateral flexor synergy. Progression is easily obtained from the capsule; and the pleasure reaction has developed twice, once out of contralateral fore-leg flexion lateral to the head of the caudate, once out of ipsilateral fore-leg flexion excited mesially. This latter instance is noteworthy because the medial extrapyramidal motor field from which the fibres here excited almost certainly derive, has never yielded more than the primary movement. In the totally decorticate and unanæsthetized animal the reaction of striking obtained from the anterior limb becomes an unmistakable rage reaction. Between the thalamus and the mid-brain, however, all this variety of motor activity disappears from the pes, except for an occasional and ephemeral flexion-protraction extension sequence from the most medial part. The tegmentum of thalamus and mid-brain together yield all the patterns of cortical extrapyramidal action, but equally well whether the descending cortical systems be intact or degenerated. Again, therefore, the brain-stem response depends upon intrinsic brain-stem structure, which may or may not be the structure upon which the cortex acts.

To analyse the brain-stem motor mechanism is outside the scope of the present study, but several generalizations from the mass of data accumulated are needed for discussion later. In the first place, the complicated performances of unmistakable significance, such as progression, the pleasure reaction, striking and placing, have been obtained as well-integrated acts only with a level of section which conserves the posterior part of the hypothalamus and the greater part of the ventral thalamus and subthalamus. The dorsal level of transection is immaterial. On the other hand, all the movements described as primary to these performances have been obtained in specific regions of the mid-brain. And on continued stimulation these may reverse, and even alternate haltingly, although the act in its perfection of integration is not produced. With successively more posterior brain-stem transections, the primary or postural quality of the movements produced intensifies, and the rhythmic element weakens.

The endeavour to track down and analyse the subcortical basis of cortical extrapyramidal action has been fruitful largely in showing the difficulties in the way of such study. The virtual inactivity of the peduncles has been quite unacceptable in view of the fact that Weed (1914) has described an ipsilateral inhibitory action in their mesial fraction, which is almost certainly that of the anterior tone inhibiting field, and Warner and Olmsted (1923) a contralateral inhibitory action which may be that from the posterior field. Throughout the mid-brain the complex, unstable and highly variable motor activity of the tegmentum contrasts strikingly with the meagre activity of the peduncles, yet these contain the largest intact descending cortical systems, those to the pons. Surely peduncles, pons and cerebellum must participate in cortical extrapyramidal motor action, but the manner of this participation must be left to future experimentation.

Conduction through the Medulla.

The attempt to determine the site of the conduction through the medulla of the cortical activities which survive pyramid section, was undertaken both as a control on the possibility that aberrant pyramidal fascicles which escaped the lesion were involved, and with the location of the more important descending extrapyramidal pathways in mind. Extending the lesion at the trapezoid level deep and laterally, tripling its cross-sectioned area, made no further inroad upon cortical function. Projecting the lesion deep along the mid-line to within a millimetre of the floor of the 4th ventricle also had no appreciable further effect. But extending this deep midline lesion laterally, through the central part of the tegmentum and into its ventrolateral angle, weakened or abolished the inhibitory action of either cortex upon tonic extension in the extremities of that side, and greatly reduced the cortical motor activity. If these lateral sections penetrate directly in at the trapezoid level, or are directed somewhat cephalad, and if they do not penetrate the fourth ventricle, tonic extension will remain sufficient to serve the examination, and sometimes in even greater intensity than before. Sections which penetrate the ventricle, or sections placed below the trapezoid level usually increase tonic extension in the contralateral legs, but produce in the legs of the same side a tonic flexion which is likewise not relaxed from the cortex. Through all these procedures the action of either cerebral cortex upon the extremities opposite to the medullary lesion remained essentially as before. At the medullary level, therefore, the extrapyramidal activity of cortical origin has in very large part its final relationship to the same side of the body, in contradistinction to pyramidal activity which has yet to cross. Furthermore the lateral part of the tegmentum appears to play a larger role in extrapyramidal conduction than does the medial part. More than this cannot be said.

DISCUSSION.

Cortical extrapyramidal function has, as it were, three spatial co-ordinates; it is distributed horizontally over the surface of the cortex and it is projected vertically into the brain-stem. The anatomical structure which is the framework of this function likewise has surface and projected aspects. Unfortunately the analysis of this structure requires the application of two techniques: cyto-architectural study of the cortex and study of fibre degeneration into lower levels; and no one individual has, so far, applied the two adequately to the analysis of any part of the cat's cortex, far less to the whole. Scattered information on both aspects of structure has, however, been collected from the literature, and will be put together to illustrate both what may be surmised of the relationship between structure and function in cortical extrapyramidal action, and what still remains entirely obscure.

In the frontal region where the cyto-architecture of the cortex has been most studied, certain of the extrapyramidal activities lodge unmistakably in distinct formations. Thus each of the major subdivisions of this region, the area of giant pyramids, the area frontalis agranularis and the prefrontal region, has its characteristic inhibitory action, although broad zones of overlap prohibit too sharp distinction. On the other hand the last of these fields is matched in this action by another field in the sylvian region, yet in structure the two are quite dissimilar. In such a case the complexities of cyto-architecture may very well conceal a common structural element which underlies the like action, and dissimilar features support other aspects of function not possessed in common by the two. Study of subcortical projection is more likely to disclose the common structural element.

The extrapyramidal motor fields again illustrate the tendency for structural distinctions to conform with functional distinctions. Figs. 5 and 6 show the cranial and extrapyramidal motor areas in the cat's brain; and Brodmann's (1905) map of the area gigantopyramidalis in the cat. The correspondence is striking. Unhappily Brodmann has nowhere published descriptions or pictures of the material from which this map was drawn to illustrate the meaning of the term "gigantopyramidalis." Obviously since the field contains the centres for rhythmic licking and chewing and the frontal adversive field, the area is not homologous with his Area 4 in primates. Most likely it takes in all the cortex with motor characteristics in the frontal region. Within this large field certain of the known structural entities correspond further with localized components of function. Thus, that part of the peri-cruciate area which probably is homologous with the primate Area 4, yields a characteristic extrapyramidal motor activity which conforms with the usual allocation of the area to fore and hind-legs.

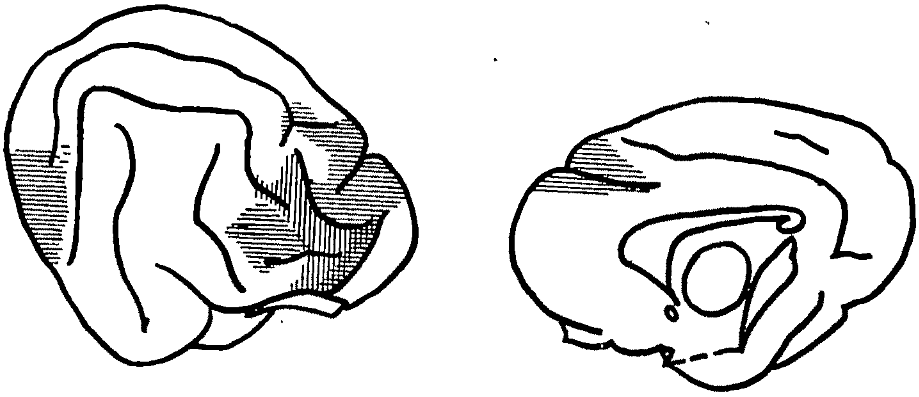

FIG. 5.—Total cranial and extrapyramidal motor areas of the cat's cerebral cortex.

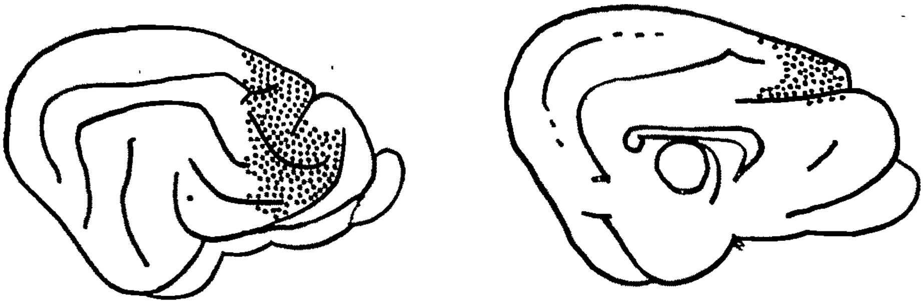

FIG. 6.—Brodmann's (1905) map of the area gigantopyramidalis in the cat.

And the medial extrapyramidal motor field would, perhaps, lie within the area frontalis agranularis were this fully known.

The placement of the extrapyramidal fields in the cortex is not haphazard. All the relatively undifferentiated cortex is given over to the function of inhibiting movement, which suggests that this function is not only widespread, but also very primitive. The field for this activity encircles the hemisphere on its medial aspect, spreads on to the tentorial surface of the hemisphere, and extends thence laterally along the rhinal fissure, to reappear on both sides of the sylvian fissure in the very strongly acting lateral field. Here a high degree of cytoarchitectural differentiation proves that this function does not necessarily lodge in undifferentiated cortex. Within the circle of this inhibitory function three fields of sensory reception are recognized, for general somatic sensibility, for sight and for hearing. The two largest motor areas lie in conjunction with these. Both fields produce the same range of extrapyramidal motor action, though not in equal strength, which may represent simply access to the entirety of the brain-stem motor mechanism. The frontal motor area develops in addition a unique motor system, the corticospinal. And the inhibitory mechanisms effective against tonic contraction are either localized exclusively here, or represented only here in sufficient strength to be dissociated from motor function. The placement of the small lateral extrapyramidal motor field is without obvious significance.

For its action upon the brain-stem the cortical extrapyramidal function has available an anatomical structure of great complexity, put together, apparently, on the principle that each cortical area shall be connected with many subcortical levels. Thus the variable complexity of action which is so conspicuous a feature of the mechanism in action may be provided for, or the multiple functions which are localized in any one region of cortex may each find separate subcortical projection. Unfortunately, few of the studies of Marchi degeneration from cortical lesions in the cat qualify as the complete study of the subcortical projection of a cortical area which is structurally or functionally a unit. Either the cortical destruction was widespread, as in Probst's and Poljak's otherwise excellent work, or the study of the brain-stem seems to have been inadequate. In particular have lesions in the "motor" or "sigmoid" region been large and uncontrolled. These studies are, moreover, subject to the limitation of Marchi technique, that only myelinated fibres are demonstrated, and only so far as they are myelinated. Terminations are therefore frequently uncertain. Furthermore, McKibben and Wheelis (1932) have already demonstrated that unmyelinated fibres form a considerable part of the pyramidal projection, and the shorter and phylogenetically older systems to the brain-stem may well consist of such fibres in even larger proportion.

As they stand, however, the recognized fibre connections of the cortex appear to have significance. To begin with, the "sigmoid" or "motor" area, which produces the largest variety both of motor and of inhibitory actions, projects onto virtually every motor centre of the brain-stem with the exception of the globus pallidus, the hypothalamus, and, surprisingly, the nucleus ruber. Probst (1901) and Simpson (1902) together describe fibres to the caudate and lentiform nuclei; to the ventralis anterior, ventralis a, lateralis b and medialis c of the thalamus: to the subthalamus and "corpus albicans" (?); to the superior colliculus, substantia nigra and tegmentum of the mid-brain; to the pontine nuclei; and to the reticular formation of the medulla. On the other hand, the posterior motor area, which has motor function only, and that in lesser strength, has a correspondingly more limited projection (Barris, 1936), to the pretected area, superior colliculus and pons. That projection to the tegmentum bulks large from the sigmoid area and is lacking from the occipital motor field, is of interest in connection with the tendency for the occipital field to yield complete acts or nothing, whereas the sigmoid area readily yields the simple movements called primary, which are so characteristic a result of direct tegmental stimulation. Projection to the pons is seemingly a common element in all motor projection.

From the area frontalis agranularis the only projection described, except for corticospinal fibres, is into the pons, but there is no indication in the text of either of the investigators who have studied this matter (Langworthy, 1928; Olmsted and Logan, 1925) that they examined more than the peduncles, pons and pyramids. A cortico-pontine, ponto-cerebellar, cerebello-dentate, dentato-tegmental, tegmento-spinal system might well serve the motor activity of the cortex in question, for the long course through a second cortex would account for the rarity with which the activity is obtained. On experimental grounds Weed (1914) and Warner and Olmsted (1923) send the inhibition which they find obtainable in the basis pedunculi into the pons, and thence to the cerebellum. The outstanding viability and resistance to anæsthetization of the inhibitory action obtained in the present study from the area frontalis agranularis, argue strongly against such complicated projection, particularly against circuit through a second cortex, and for direct action, and raise the question of possible collateral action from the cortico-pontine or ponto-cerebellar fibres into Deiters' and the reticular nuclei. The pupillo-dilator and adversive actions which are found in the anterior border of the area, perhaps constituting an area homologous with the primate Area 8, also seem to be poorly provided for in an exclusively cortico-pontine projection.

The frontal and lateral fields for inhibition of movement have in common projection both to the striatum and to the caudal and ventral thalamus (Riese, 1924, for the gyrus proreus, and Poljak, 1927, for the

" insular region "). The connection with the striatum is the unique feature in this projection, but the projection on to those portions of the thalamus which may be the seat of pattern formation in motor activity has possibly more obvious significance. This variety of cortico-thalamic connection is, moreover, the most widespread projection from the cat's cortex, matching the distribution of the " quieting action." In Probst's series of studies of Marchi degeneration from the cat's cortex, the only area not having this projection was the striate area.

The organization for action within this elaborate structure demands consideration. Cortical extrapyramidal function presents two aspects, excitation and inhibition, which are in part co-operative and in part antagonistic. When they are most co-operative, as in the case of inhibition of tonic contraction preparatory to movement, they are localized together. When they are antagonistic, as in the production of rhythmically repeating performances and the arrest of these, they are localized separately. In the peri-cruciate region the motor and inhibitory activities are disposed in pairs, the motor action complementing the inhibition, usually at a higher threshold. This raises the question as to the extent to which the two are served by the same subcortical projection, perhaps by collateral connections with different subcortical centres; to what extent by entirely separate neurones? In the Betz-cell field where extrapyramidal activity, both motor and inhibitory, co-exists with corticospinal activity, and all three are obviously co-ordinated both in distribution and in function, some collateral action seems in order because the collaterals are known. On the other hand, the large number of small pyramidal cells distributed among the Betz-cells can certainly provide origin for any number of quite independent prespinal projection systems. And the close correspondence of pyramidal and extrapyramidal action may represent, not inevitable co-function under the all or nothing law of an enormous unit with prespinal and spinal termination, but close correlation between discrete neurones of pyramidal and extrapyramidal character. This latter organization should provide better for the lability which characterizes cortical action. Both arrangements may well be utilized, separately and together, to different ends.

Although the fields for inhibition of movement have been devoid of projected somatic motor action, if they contain Hughlings Jackson's " highest motor centres," the principle of co-ordinated or reciprocal motor and inhibitory action, may again be exemplified. The inhibitory action would then be conceived of as arresting activity in being to make way for activity newly conceived, or perhaps for voluntary inactivity. But in this case "the highest motor centre" stops activity by direct projection while it utilizes "the middle motor centres," or motor area proper, to execute its new project. In the cat, the poor differentiation of the prefrontal area restrains such speculation, and perhaps this almost rudimentary cortex has as its chief or entire rôle, projecting the cortical function of attention. In primates Jacobsen's (1935) recent studies have dealt with just such a level and locus of motor organization as that here pictured, and Richter and Hines' (1936) report of the production of excessive activity by bilateral removal of the prefrontal areas, supplies the other half of the co-ordinated whole. A striking feature in the aimless activity of the monkeys, operated upon by Dr. Hines is their conspicuous failure to fix attention upon a stimulus before going into action. The animals lack just that reaction of fixation at attention which appears so unmistakable on stimulating the cat's prefrontal area.

At first sight the inhibitory activities of the cerebral cortex appear simpler than the motor activities, and the inhibition which stops all movement the simplest of all. But the initial problem presented by such action—where in the neural axis is activity stopped, whether at its source in the brain-stem or at the final motor neurone in the cord—remains without clear answer. It has been argued that movement is probably stopped where pattern is formed, because tonic activity in muscle is not affected. And the widespread projection to the caudal and ventral thalamus seems to provide a suitable avenue for such action. The effect on respiration offers the greatest challenge to experimental analysis because there are three obvious levels where this might operate; in the terra incognita of the striatum, in "the vegetative centres" of the hypothalamus, or on the respiratory centre in the medulla. Tracts which inhibit respiration have been identified in the mid-brain, on the mesial edge of the basis pedunculi, but whether these come from the cortex or not the evidence does not determine.

The inhibitory actions on tonic contraction in the musculature also fail to yield even the first answer to probing. It is not certain at what level the inhibitory process is brought to bear against the excitatory. The viability and resistance to anæsthesia of the inhibition from the anterior field have been used to argue that that action must be direct, probably without relay. And if this argument is valid, then the action is prespinal because no extrapyramidal fibres pass to the cord. But this is not evidence. One thing only is certain—the rubrospinal system is not inhibitory to the cord in the manner required. Repeated careful stimulation of the red nucleus and its tract throughout the mid-brain and pons, and under the varied conditions of stimulation employed to bring out the inhibitory component in the tegmental reaction, has always yielded motor activity, flexion of the extremities with lateral curvature of head, body and tail, or nothing. The reticulospinal tracts should be investigated. Tentatively, however, it has been concluded that the powerful and viable action of the anterior inhibitory field probably represents direct action by a system of single neurones upon the tone-producing centres of the rhombencephalon.

The organization of cortical extrapyramidal motor action presents again, insistently, the problem to what extent is complexity of action dependent upon the correlated action of separate neurones, to what extent upon collateral action into different brain-stem levels from one descending system of neurones. The exactitude with which the building up of extrapyramidal motor activity from the primary movement to the significant performance with lightening anæsthesia, resembles the disintegration of motor action directly excited from the brain-stem with progressively lower transections, suggests that the building-up process represents the recruitment of successively higher levels in the brain-stem. But independent neurones or collaterals might equally well accomplish this, or both working together. The problem recurs in the homogeniety of action of the cortical extrapyramidal motor fields at a given time, and their different action from time to time. Does each pattern of response possible in a given field utilize a separate subcortical projection system, or is one projection system with wide subcortical connections capable of evoking one or another response depending upon conditions at lower levels? The first allows for choice of action at the cortical level; the second apparently does not. In either case the pattern which dominates extrapyramidal motor activity is probably constructed, not in the cortex, but beneath, for the activities in question are those which a decorticate cat executes in stereotyped fashion, so that patterns of action must be complete in the lower centres. The author has been privileged to examine Dr. Bard's decorticate cats, and has seen in these beautifully prepared and well-kept animals every one of the activities in question. The cortical extrapyramidal motor mechanism may therefore be conceived of as facilitating activity in lower centres, even as initiating it, but as determining form only by a limited selection of one or another pattern intrinsic in lower centres. This pattern is then unmodifiable from the cortex, after the pyramids are cut, except by the interaction of conflicting projection.

The relationship between pyramidal and extrapyramidal action from the cortex must finally be considered. The range and strength of activity obtainable from the extrapyramidal mechanism alone make the function of the corticospinal system, which cannot be similarly isolated in the cortex, difficult to decipher, but judging from the results obtained on stimulating the medullary pyramids, the contribution of the corticospinal system to total function is essentially motor. All the action which the cortex yields with this system intact has been obtained at one time or another with the system cut. Yet with the pyramids cut movements tend to be complex synergies, involving at least a whole extremity, and often the entire animal, whereas with the pyramids intact almost any fraction of such a large movement except extrusion of the claws may, with threshold stimulation and a little searching for the proper cortical point, be isolated. The corticospinal system therefore makes possible what may be called "fractionation" in motor function. A second contribution of corticospinal function, related to the first, shows in comparing results of cortical stimulation in anæsthesia light enough to permit extrapyramidal action, with the pyramids intact and cut. The comparison may be made either successively, before and after bilateral pyramid section, or simultaneously, on the two sides with a unilateral lesion. With the pyramids cut an extrapyramidal motor field gives the same reaction throughout, the threshold only varying. With the pyramids intact a slight shift in the point of stimulation in the Betz-cell field may modify, slightly or radically, the form of the recognizable patterned response, introducing perhaps more or less adduction or abduction, emphasizing action at one joint over the others, or interfering with the smooth sequence. Thus the intact corticospinal system obviously provides for the modification in pattern which the extrapyramidal mechanism so conspicuously lacks. The third and probably most important contribution of the corticospinal system to total function is a low threshold. In acute experiments the rise in threshold after pyramid section involves an element of shock, for it is not confined to the Betz-cell area. But study of surviving preparations (Tower, 1935) has demonstrated how general and profound and enduring is the loss of excitation in the segmental motor mechanism of the cord when corticospinal function is abolished. The corticospinal system thus underlies two exceedingly important elements in total function: discreteness of action, showing either as fractionation or as modification of pattern, and low threshold. The first enables the patterned reactions of the extrapyramidal motor mechanism to be applied accurately to meet a situation, the second contributes speed and strength to the execution.

SUMMARY.

Widespread areas of the cat's cerebral cortex appear to be a source both of excitation and of inhibition throughout the length of the cerebrospinal axis. The motor function of the cortex is organized in two major parts. The corticospinal tract and the homologous tracts to the brain-stem operate directly or through an internuncial neurone on the final common path to the effectors; the extrapyramidal motor function operates indirectly, by facilitating the activity of lower brain-stem mechanisms in which the form of the activity is determined. Yet this distinction between pyramidal and extrapyramidal modes of operation is more apparent than real. For section of both corticospinal tracts in the cat diminishes initiative and slows initiation and performance, but destroys no recognized element of the animal's activity, although the residual activity becomes stereotyped. Hence the pyramidal tracts likewise appear merely to facilitate and to modulate the patterned activities of the lower motor mechanisms, but at the final segmental level rather than at the source.

The inhibitory function of the cerebral cortex is dominantly extrapyramidal. Reciprocal inhibition probably enters into corticospinal function as a property of the intrinsic cord mechanism upon which this system must act, but no independent inhibitory action has been found in the system. The cortical inhibitory mechanisms probably act on the brain-stem motor mechanisms engaged in producing movement or tone. Those effective against tonic contraction are localized and integrated with motor mechanisms, but are characterized by lower threshold. The inhibition effective against movement is the most widespread activity demonstrable in the cortex, possibly representing a general cortical function.

The total organization of pyramidal and extrapyramidal action may perhaps be conceived somewhat as follows. The mechanism upon which the cortex acts is organized in four levels. The segmental level is at the same time both the initial and the final site for integration. It projects to the periphery. The lower brain-stem motor mechanism constitutes a level for reintegration and for producing the elements of posture and movement. It projects on to the segmental mechanism. The thalamic (or thalamo-striatal?) motor mechanism constitutes a level for further integration and for pattern formation, and projects on to the lower brain-stem mechanism, and not on to the segmental mechanism. The cerebellum will have to be left out of consideration. The cerebral cortex represents the highest level of integration, and projects on to each of the three lower levels. To the segmental level this projection is dominantly excitatory; to the higher levels excitation and inhibition are fairly equally matched. Altogether the cortical mechanism is able both to facilitate and to inhibit activity throughout the neural axis, either at the source or at the segmental level. This is, however, projected action. The prime function of the cortex itself must be so to integrate activity in these many projection systems that the final product of excitation and inhibition in the lower centres results in activity and cessation of activity in the effector mechanism, appropriate to the situation to be dealt with.

REFERENCES.

Barris, R. W. *Journ. Comp. Neurol.*, 1936, **63**, 353-368.

Brodmann, K. *Journ. f. Psychol. u. Neurol.*, 1905, **6**, 108-120.

Bubnoff, M., and Heidenhain, R. *Pfl. Arch. f. Physiol.*, 1881, **26**, 137-200.

Campbell, A. W. "Histological Studies on the Localization of Cerebral Function." Camb. Univ. Press. 1905.

Foerster, O. *Lancet*, 1931, **ii**, 309-312.

Hering, H. E., and Sherrington, C. S. *Pfl. Arch. f. Physiol.*, 1897, **68**, 222.

Jacobsen, C. F. *Arch. Neurol. and Psych.*, 1935, **33**, 558-569.

Langworthy, O. R. "Contrib. to Embryol.," Carnegie Inst., Wash., 1927, **19**, 177-207.

Idem. Bull. Johns Hopkins Hosp., 1928, **42**, 20-66.

McKibben, P. S., and Wheelis, D. R. *Journ. Comp. Neurol.*, 1932, **56**, 373-390.

Myers, J. *Journ. Lab. and Clin. Med.*, 1936, **21**, 949-952.

Olmsted, J. M. D., and Logan, H. P. *Amer. Journ. Physiol.*, 1925, **72**, 570-582.

Poljak, S. *Journ. Comp. Neurol.*, 1927, **44**, 197-258.

Probst, M. *Arch. f. Anat. u. Physiol.*, Anat. Abth., 1901, 333-356.

Idem. Ibid., 357-370.

Idem. Jahrb. f. Neurol. u. Psych., 1901, **20**, 181-291.

Idem. Arch f. Psych. u. Nervenkrankh., 1902, **35**, 22-48.

Richter, C. P., and Hines, M. Int. Congr. Neurol, London, 1936, Abst., 87.

Riese, W. *Journ. f. Psychol. u. Neurol.*, 1924, **31**, 81-122.

Rioch, D. McK., and Rosenblueth, A. *Amer. Journ. Physiol.*, 1935, **113**, 663-676.

Simpson, S. *Int. Monatsch. f. Anat. u. Physiol.*, 1902, **19**, 304-334.

Tower, S. S *Bull. Johns Hopkins Hosp.*, 1928, **43**, 237-256.

Idem. Brain, 1935, **58**, 238-255.

Vogt, C., and Vogt, O. *Journ. f. Psychol. u. Neurol.*, 1919, **25**, 278-462.

Ward, J. W., and Clark, S. L. *Journ. Comp. Neurol.*, 1935, **63**, 49-64.

Warner, W. P., and Olmsted, J. M. D. *Brain*, 1923, **46**, 189-199.

Weed, L. H. *Journ. Physiol.*, 1914, **48**, 205-227.

OBSERVATIONS ON THE HISTOPATHOLOGY OF THE CEREBRAL LESIONS IN DISSEMINATED SCLEROSIS.[1]

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THE literature on the pathology of disseminated sclerosis is very extensive and includes able reviews by Siemerling and Raecke, Dawson and Jakob. There is, however, no general agreement on the pathogenesis of the disease, on its relationship to other demyelinating diseases, or even on various aspects of its histopathology. Experimental work has done little to settle these questions, as the pathological picture of disseminated sclerosis has never been exactly reproduced in animals.

The present communication deals with certain points of histopathology some of which have been the subject of recent controversy, while others have received scanty notice in the literature. Its object is to define more exactly the pathological picture of disseminated sclerosis in the hope of obtaining more insight into the pathogenesis of the disease.

Material.—The present paper is based on the study of thirteen cases of disseminated sclerosis the clinical course of which ranged from two months to over ten years. Only cerebral plaques were studied, and no spinal cord lesions are included in the present report. The method of study was to use frozen sections exclusively, each block being stained by all of the following methods: Scharlach R and hæmatoxylin, victoria blue for neuroglia fibres, Hortega's double impregnation for neurofibrils, Hortega's method for connective tissue and the Weil stain for myelin, or some modification thereof. On occasions other methods were also used, such as the Gros, da Fano, Perdrau and modified Cajal impregnations. The total number of plaques in this series is over 125. An exact number cannot be given since, in cutting through a block 2 to 3 mm. in thickness a few of the smaller plaques might be present in some sections but not in others.

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[1] This work was done while Dr. Lester S. King was holding a Moseley Travelling Fellowship of the Harvard University Medical School.

LIPOIDS.

The Scharlach R and hæmatoxylin stain undoubtedly gives more information concerning a plaque of disseminated sclerosis than does any other single staining method, exhibiting in a single preparation cells, myelinated fibres and many types of lipoids. Only with a fat stain can the age of a lesion be satifactorily estimated.

The destruction of myelin in disseminated sclerosis may be divided into several stages. In the earliest the staining reaction with hæmatoxylin is retained, as is demonstrated by any of the hæmatoxylin methods for staining myelin. This stage is seen in fresh plaques of a very intense nature, in which there is at the periphery of the lesion a "wall-formation" of gitter cells densely packed against the still normal myelin. In this type of plaque the lipoid in the wall of gitter cells stains with the laked hæmatoxylin, although the centre of the plaque does not. Conversely, with the Scharlach R the centre of the same plaque is bright red, while the wall-like formation at the periphery stains a feeble and dull rose or not at all. But hæmatoxylin staining lipoids are also found in fresh plaques of a much less intense nature, for example, they were seen in recent lesions of an old (ten-year) chronic case.

The hæmatoxylin-staining lipoids are of two sorts. There is the typical "Markball," large in size and staining practically the same colour as normal myelin, of the type described in Wallerian and other types of degeneration. There are also much smaller granules, more or less pale blue in colour, contained within typical fine-latticed gitter cells, and in no way to be confused with "Markballen." It is these fine pale droplets which are of special significance in this study.

The usual early plaque shows a dense and even distribution of Scharlach-staining lipoids. Plate X, fig. 1, shows such an early plaque in a hæmatoxylin-Scharlach R stain. Much of the fat is contained within typical well-rounded gitter cells, but much of it lies within phagocytes that have not yet reached the gitter-cell stage. Furthermore, there is a relatively large amount of fat which is completely extra-cellular, lying in varying-sized droplets in the interstices of the tissue. It will be noticed that there is no special aggregation of fat around the two blood vessels lying across the middle of the photograph.

The age of the lesion in fig. 1 is probably about 2 to 3 months. This particular patient died four months after the onset of symptoms, and since other plaques from the same case showed a much more advanced stage of katabolism of lipoids we must conclude that fig. 1 represents a duration somewhat less than that of the illness. The picture, however, differs in no particular from fresh plaques of old chronic cases.

What may be called the second stage of the katabolic process begins with the perivascular accumulation of lipoids. Often the perivascular spaces are so heavily loaded with gitter cells that no other cell type can be found. But, especially when the process is somewhat further advanced, other types can be seen. Apart from lymphocytes and some plasma cells, large numbers of pale mononuclear cells may be observed, with nuclei of somewhat irregular shape and only moderately rich in chromatin, and with pale irregular cytoplasm. Such cells contain fine fat granules ranging in number from one or two to a dozen or more. Sometimes there are long spindle-shaped cells with a single fat granule at either pole. The cells which phagocytize lipoids in the perivascular spaces are very similar to those that store trypan blue in inflammatory reactions of the nervous system. These phagocytic cells, which are not compound granular corpuscles, are evidently mesodermal cells, probably partly of blood and partly of connective tissue origin.

The disposal of fat from the lesions appears to take two forms. One is the actual passage of fat-laden cells into the perivascular spaces, where they degenerate, giving up their contents to new fresh cells. Secondly, a certain amount of free fat finds its way in the tissue currents to the perivascular spaces, and is there taken up by young phagocytes in situ. It is almost inconceivable that the fully rounded, fat-laden gitter cell has any power of active migration such as we ascribe to the tuberous and amœboid forms of microglia. The gitter cells in the perivascular spaces may have been carried there passively, as Hassin suggests, in the tissue currents, or may have arisen in situ from the maturation of undifferentiated cells and the phagocytosis of passively carried extra-cellular fat.

This second stage, with the accumulation of perivascular fat, occasionally sees the presence of hæmatoxylin-staining lipoids in the intervascular tissue. Such relative persistance of an early form of myelin breakdown requires a well-controlled experimental approach for its elucidation.

In the third stage there is a gradual disappearance of fat, first from the tissue between the blood vessels, and finally from the blood vessel sheaths themselves. The gitter cells in the tissue become fewer and more widely spaced, the free extra-cellular fat disappears. In this third stage there may be a large number of fine lipoid droplets contained within cells which bear a morphological resemblance to young microglia. Each cell contains only a few droplets. The origin of these cells, appearing as they do after the compound granular cells have already disappeared, requires further study.

An unusual form of myelin breakdown has been observed, especially in the more recent lesions. Scattered through such plaques in sections stained for fat, are rows of large, bright red globules, such as are illustrated in Plate X, figs. 1 and 4. At first glance such rows of globules appear to be long rod cells crammed with fat. But a comparison with fig. 3 shows this not to be the case. Fig. 3, taken from a fresh cortical plaque, shows rod-shaped microglia filled with fine fat granules. Plate XI, fig. 7, is at the same magnification. The individual fat droplets are enormously larger, and the total length of a chain of these averages about three times the length of the rod cells. Furthermore, in the white matter, where alone such degenerating fibres are found, phagocytic rod cells do not occur.

This is no evidence that these long rows of fat globules have been affected by intracellular digestion. Their conversion from myelin into brilliantly Scharlach-staining lipoid has occurred extracellularly, without phagocytosis. The lipoid masses are large in size, and remain in a straight line, in the original position of the fibre. The fat droplets of this form of myelin degeneration are brilliantly doubly refractile when examined with crossed Nicol prisms. We interpret these structures as myelinated fibres which have become transformed into simpler lipoids without the mediation of cellular activity. The mechanism of this change, which seems to be somewhat different from anything ever described for secondary degeneration, we cannot explain, but we wish to record the observation.

The doubly refractile lipoids in multiple sclerosis are very abundant, especially in the first, second, and early third stages of the katabolic process. Several different forms may be distinguished. (1) Different sized globules which show the typical myelin cross. These are presumably myelin droplets which, in spite of staining bright red with Scharlach R, are but little altered from their original chemical constitution. (2) Globules and irregular masses which, through the crossed Nicol prisms, appear doubly refractile in a bright red hue. These appear to be fatty acids either free or in combination. (3) Needles and fine droplets which are doubly refractile without a trace of colour under polarized light. These probably are cholesterol. (4) Mixed masses appearing partly red and partly white. (5) Scharlach-staining material which is invisible under polarized light.

The fat-laden field, appearing fairly uniform with ordinary illumination, is broken up into these various constituents by crossed Nicol prisms. The cholesterol, which does not stain with Scharlach, is masked by other stainable lipoids, and its true nature is brought out only by polarized light.

The relative and absolute amounts of doubly refractile lipoids varies according to the age of the plaque. In fresh plaques the proportion of anisotropic to isotropic lipoid is illustrated in figs. 1 and 2 which are of the same field, at the same magnification, but with fig. 2 taken under polarized light. A certain amount of the doubly refractile material is somewhat out of focus, but the two photographs may well be compared.

In somewhat older plaques the total amount of Scharlach-staining material is much less than in fig. 1, but the quantity of doubly refractile lipoids may be the same as fig. 2. In other words, in the older plaques the proportion of the doubly refractile lipoids is much higher than in the fresh plaques. This suggests either that certain of these lipoids are specially resistant to the katabolic process, or that lipoids become for a time more strongly anisotropic as they break down.

It may be mentioned here that doubly refractile lipoids are very infrequently found in cortical plaques. Further, the lipoid which is contained within ganglion cells, whether in the cortex or other gray matter affected by multiple sclerosis, is not doubly refractile.

A great many different shades of red are observed with the use of Scharlach R, especially a light yellow, a dull rose, a dull brick-red and the more typical brilliant light red. These shades, without question, correspond to differences in the chemical composition of the lipoids. Some of them, in such diseases as diffuse sclerosis or amaurotic family idiocy, are frequently called prelipoids. This subject cannot be thoroughly understood without a new experimental approach, since the data at hand are not adequate.

For literature in connection with this section, reference may be made to Hurst, Toyama, Greenfield, Scholz and Kaltenbach.

AXIS CYLINDERS.

In the demyelinating diseases certain morphological changes in the axis cylinders are well known, especially diffuse œdematous swelling of the entire fibre, and local fusiform thickenings and node formation. Certain other changes have been entirely neglected in the English literature, although they have received some attention in the German and French journals.

Marinesco and Minea, Doinikow and Jaburek, working with spinal cord lesions in multiple sclerosis, have described certain formations which are interpreted as regenerative phenomena. The formation of nerve sprouts, end bulbs and end loops, *boules de retraction* and various other types of loops, swellings, buttons and ball formation, are of the same types as are seen in regenerating nerve tissue in the peripheral nervous system. Some of these structures, especially *boules de retraction*, whether attached to nerve fibres or cast off free in the tissue, are essentially degenerative phenomena. Others are regenerative. The appearances of degeneration and regeneration are closely connected. The general morphology of nerve-fibres undergoing degeneration and regeneration is beautifully illustrated in Cajal's monograph. Vol. II, dealing with the central nervous system, is of especial interest.

In multiple sclerosis, the authors quoted have been concerned with spinal cord lesions. Doinikow studied cerebral plaques but could not stain them successfully. He admits that the spinal cord is very much easier to stain in this respect than is the cerebrum. Consequently special interest attaches to the finding, in the present series of cerebral plaques, of such regenerative phenomena.

The most frequent type is that illustrated in Plate XI, fig. 6. Finely calibered nerve fibres terminate in small loops which may be present in great profusion. These loops resemble the synaptic *boutons terminaux* of neurones. In multiple sclerosis there are various transitions from a loop to a solid club, but the former are overwhelmingly more numerous. Isolated cast-off balls are found occasionally. Sometimes the terminal loop consists of a fibrillary whorl like the neurofibrillar change of Alzheimer on a small scale. A frequent observation is the appearance of a loop, not terminally, but in the course of a fibre. This greatly resembles the *bouton de passage*, one type of synapse found normally and fairly easily on anterior horn cells of the spinal cord.

Plate XI, fig. 5, from a shadow plaque, and at less than half the magnification of fig. 6, represents a different type. The swelling and œdema of the long stretch of nerve fibre is an undoubted regenerative appearance. So, too, is the enormous "bomb" terminally, for it is much too big to be a so-called terminal club. It might be called a large *boule de retraction*. The constriction just below the spherical enlargement is probably a sign that the retraction ball will shortly be cast off free in the tissue. However, there are visible several small collateral sprouts, which must be interpreted as regenerative. This is an example of the close relations between degeneration and regeneration.

The "terminal" type of regeneration, as shown in fig. 6, is of much more frequent occurrence in the cerebrum than is the "collateral" sprouting in fig. 5. In the spinal cord Marinesco and Minea (1909) found the opposite to be true. From the literature on the subject it appears, too, that the terminal loops are not nearly as frequent in the spinal cord as in the cerebrum.

The regenerative phenomena described here are found in both new and old plaques, but are much more frequent in recent lesions. This is only to be expected in view of all the known facts of regeneration *cf.* Cajal). These appearances have also been observed in a wide variety of other conditions (Marinesco and Minea (1910), Doinikow, Beilschowsky (1909)). We have found them also in certain cases of diffuse sclerosis, as has Jakob (1914).

The number of new and functioning fibres in disseminated sclerosis that are the result of regeneration is probably extremely slight. In the earlier literature Strähuber believed that the greater number of axis cylinders found in multiple sclerosis were the result of regeneration, the original fibres having been destroyed by the earlier stages of the disease process. Bielschowsky was able to show that these conclusions of Strähuber were due to an inadequate histological technique, a contention that the passage of time has fully confirmed. The undoubted regenerative phenomena that are found are important for the general pathological physiology of nerve fibres, and are not of clinical significance.

The type of degenerative phenomenon appearing in the cerebellum is shown in Plate XI, fig. 7. The "torpedo"-like enlargement forms on the axones of the Purkinje cells. This has previously been observed by Doinikow and by Marinesco, in this as well as in other conditions. This pathological feature in a number of conditions excluding disseminated sclerosis is treated in a forthcoming paper by Aring.

In reference to the axis cylinders an interesting point was recently raised by Putnam, who, in comparing disseminated sclerosis with disseminated encephalomyelitis, stressed the frequency and intensity of loss of axis cylinders in the former. In his series of 35 plaques from 11 cases, there was complete or almost complete loss of nerve fibres in just over 50 per cent. It is true, and at the present time generally accepted, that the persistance of axis cylinders in disseminated sclerosis is only relative, and that there is a diminution in many cases. But our series, over 125 plaques from 18 cases, showed directly opposite results from Putnam's. Less than 10 per cent. showed what could be called "severe destruction," the remainder being fairly evenly divided into slight or no loss, and moderate diminution. The extreme degree was not only rare, but where present was always in tissue that was highly rarified or spongy.

What we call severe destruction is reduction in number to one-fifth or one-seventh (approximately) of the normal density of nerve fibres. Putnam's criterion is complete absence of nerve fibres in at least some high-power microscopic fields. We consider the point to be of considerable importance, since it is one of the features that may distinguish disseminated sclerosis from other demyelinizing diseases. In some cases of diffuse sclerosis the degree of axis cylinder destruction mentioned by Putnam may be found. Disseminated sclerosis cases, taken as a group, seem to be in a different category.

In two plaques of one case there was extreme softening and great rarefaction of tissue. The plaques could be cut in frozen section only after gelatine embedding. Axis cylinder impregnation was not successful in these two plaques, which are not included in the present series. But in all other plaques unembedded frozen sections were easily cut, with the results enumerated above.

The divergencies from the results of Putnam may be explained by the difference in technique. The limitations of aniline blue as an axis cylinder stain were demonstrated by Bielschowsky (1903) in his controversy with Strähuber. It has long been known that when peripheral nerves are stained by aniline blue, as in the Strähuber or Stroebe methods, the axis cylinders appear to be interrupted at the nodes of Ranvier. It seems that aniline blue stains axoplasma and not neurofibrils, and the results are therefore not comparable with those obtained by ammoniacal silver methods. Furthermore, in our experience, silver stains for axis cylinders in celloidin sections such as the Gros or Davenport modifications, are rarely as complete as a good impregnation in frozen sections. The degree to which Putnam's results are truly representative can be judged only by the publication of results in other series.

GLIOSIS.

Using the term gliosis in the sense of a proliferation of astrocytes and fibrous glia, we wish to lay special stress on the observations that overgrowth of neuroglia is one of the early reactions in multiple sclerosis.

Dawson, in distinguishing six stages in the natural history of disseminated sclerosis, places "commencing fibril formation" as the fourth step, following that of "fat granule cell myelitis." There is a tendency in the English literature to regard the gliosis as a secondary phenomenon, appearing after the destructive stages have run their course. On the other hand, in the Continental literature there is evidence that glial proliferation is of a more primary nature. The earlier views of Strümpell and Müller that the pathogenesis of disseminated sclerosis depends on a primary disease of the glia, are now definitely untenable. But both Jakob (1929) and Marinesco, for example, express dissatisfaction with the view that gliosis is merely secondary, although they do not express any definite alternative hypothesis.

The alternatives may be phrased as follows: If the gliosis is "primary" there is an essentially simultaneous action of the pathogenic agent on the nerve fibres (especially the myelin sheaths) and the astrocytes, so that both are affected by the first stages of the disease. On the other hand, if the gliosis is secondary, the pathogenic agent acts only on the myelin sheaths and the reaction of the astrocytes is contingent upon this damage. The difference is one of "simultaneous" as opposed to "successive" action. This difference is important in any attempt to define the nature of the pathogenic agent. Is it something which acts on the nerve fibres fundamentally, or does it attack the astrocytes as well?

The evidence is of two sorts. In the first place one may observe a strong gliosis in the early stages of plaque formation. There are scattered references to this in the literature. In our experience this is very definitely the case. Plate XI, fig. 8 is a victoria blue preparation of the same early plaque illustrated in fig. 1, showing clearly the swollen astrocytes and the great increase in neuroglial fibres. This gliosis is occurring in a plaque in the first stage of the process, of an age estimated at 2 to 3 months. Such an appearance is common. Victoria blue preparations should be compared with fat stains on the same lesion, and not with myelin stains as is so frequently done. Such a comparison repeatedly shows that there is a considerable gliosis in plaques which are heavily fat-laden.

In the second place, there may be a disproportion between the degree of myelin destruction and the degree of gliosis. In a group of cases of diffuse sclerosis reported by Bodechtal and Guttmann there was only a very slight diminution in the myelinated fibres, and a very heavy gliosis, altogether disproportionate to the myelin loss. In disseminated sclerosis we have observed shadow plaques with but little destruction of myelin which, nevertheless, in victoria blue preparations proved to be heavily overrun with glial fibres.

That destruction of myelin, whatever be its cause, leads to gliosis is not in dispute. For example it is a general rule that the intensity of gliosis in shadow plaques is less than in neighbouring plaques in which demyelination is complete, although this is not always true. Similarly in plaques on the floor of the 4th ventricle the gliosis is less intense in the subependymal grey matter than where myelin sheaths have been destroyed. We consider, however, that the fibrous gliosis in plaques of disseminated sclerosis occurs too early and too intensely to be merely a secondary phenomenon, although a secondary gliosis due to destruction of myelin undoubtedly also takes place.

Rod Cells and Spindle Cells.

Although "rod cells" had previously been mentioned in descriptions of demyelinizing lesions, Westphal, in 1918, was the first to describe them in detail. His histological studies of this cell type are incomplete. They were observed in cortical plaques, as well as in the white matter, in both acute and chronic cases. They were also found without demonstrable connection with plaques. In his first communication Westphal declared that there was a complete correspondence with the rod cells found in the cortex in cases of general paresis, even to the presence of right-angled branches, but he does not illustrate this point. He believed these cells to be related in some way to the vascular apparatus.

These descriptions were published before the existence of microglia as a separate entity was known, and before the microglial origin of rod cells in general paresis was established. The rod and spindle-shaped cells in disseminated sclerosis have received no further attention in the literature since Westphal's descriptions, although his findings have been widely and uncritically quoted.

In a case of Marchiafava's disease, a rare type of demyelinizing encephalopathy, reported by one of us, spindle-shaped cells were described and illustrated in foci in the white matter. On morphological evidence these cells were considered to be fibroblasts.

In the present series of disseminated sclerosis one case was encountered in which these cells were a very prominent feature. They were also observed in other cases, but not so favourably for study.

One very prominent feature in these cells is that they exhibit a definite orientation of their long axis. The cells, although at times widely separated from each other, all point in the same direction, with their long axis directed more or less perpendicularly to the margin of the plaque. Under high power such cells are illustrated in Plate XII, figs. 9 and 10. They are spindle or even slightly sausage-shaped, with elongated rather tapered nucleus containing one or two especially prominent chromatin granules. A slight concentration of cytoplasm at either pole of the nucleus passes into long delicate cytoplasmic tails. There are no lateral branches. The cytoplasm is generally compact, but may occasionally be of looser texture, shewing a few small vacuoles or dark-staining cytosomes. These cells correspond fairly well to the illustrations of Westphal.

Such spindle-shaped cells are not phagocytic. In figs. 9 and 10 the difference between these and the neighbouring gitter cells is very clear. In fat counterstains, whether of hæmatoxylin or silver stained sections, the plaques are heavily laden with fat, both in the gitter cells and free in the tissue. Nevertheless, in the midst of such an abundance of fat the cells in question are completely free of lipoid inclusions, or, extremely rarely, may contain a minute fat globule at one pole of the nucleus. Such slight amounts of fat are less than would be contained in the endothelial cells of capillaries. In marked contrast is the heavy lipoid content of the compound granular cells with which these spindle cells are intermingled.

In our material there are no transitions between the spindle cells and the compound granular corpuscles such as are seen in the microglia. Such transitional microglia are seen to the best advantage at the margin of the plaque. This is illustrated in Plate XII, figs. 11 and 12, taken from the same plaque, stained by the same method, and at approximately the same magnification as figs. 9 and 10. The difference in morphology is obvious. The microglia are multipolar, with large vacuolated pseudopodic processes, and with numerous lateral branches still apparent They are intensely phagocytic, and are pleomorphic, showing many varying stages depending on the amount of phagocytosed material. All these characters of microglia are well known, and have been frequently described and figured in many pathological processes.

The spindle cell, on the other hand, presents, in addition to a definite spatial orientation, a uniform morphology without transition, an absence of lateral branches, and an absence of phagocytic capacity in spite of the enormous amount of lipoids in their immediate surroundings.

There can be no doubt that these cells and the microglia are different types.

As to the nature and origin of those spindle-shaped cells, it is impossible to be definite. In many instances they appear to be related to the adventitia of blood-vessels, but often no such connection can be traced. So, too, is their ultimate fate unknown. They are well displayed in one early case, but in old plaques, taken from other cases, they cannot be identified with certainty; they are thus seen in one phase, and further data must await other cases or an experimental production.

In the lesions of Marchiafava's disease similar cells were called fibroblasts by one of us. We are no longer confident that this is their true nature. These cells play no demonstrable part in the formation of intercellular connective tissue substances, such as argyrophile fibres. The preparations from which figs. 9 to 12 were taken were stained by the Hortega connective tissue impregnations, which show reticulin fibres as well as general cellular morphology. Although there was a modern overgrowth of reticulin, of the type described in a separate communication, there was no correlation between this overgrowth and the cells in question. Reticulin fibres were found completely independent of these spindle-shaped cells, and *vice versa*. In other cases of this series, in which there was more marked proliferation of reticulin, these cells were nowhere in evidence. The spindle cells may indeed belong to the fibroblastic series but they do not appear to form intercellular connective tissue fibres.

We consider it more likely that the cells in question represent some type of relatively undifferentiated mesodermal cells, quite different from the microglia or the connective tissue macrophage. What potentialities they possess cannot be decided, inasmuch as later stages are not available for study.

The question remains open, how far those fusiform cells are similar to undoubted fibroblasts found in repair of brain wounds as in the experiments of Farrar and the recent paper of Hassin. Where the meninges are injured and fibroblastic proliferation is quite vigorous, cells appear which have a considerable resemblance to those described here. But the pathological conditions and the types of lesion are very different in the two cases. The entire problem of mesodermal repair in brain lesions deserves re-study with the silver techniques, with especial reference to reticulin formation.

PLATE X.

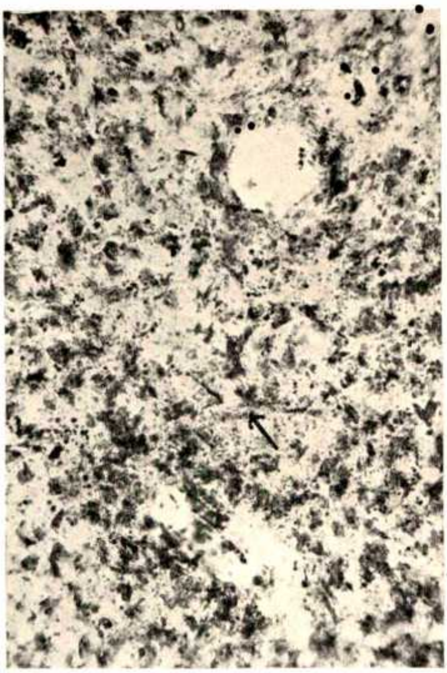

FIG. 1.

FIG. 2.

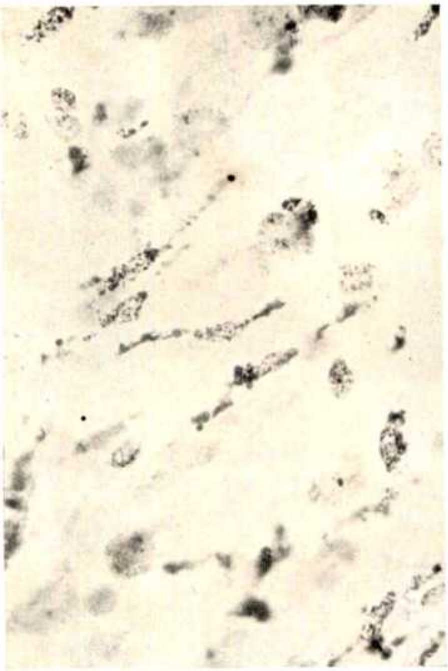

FIG. 3.

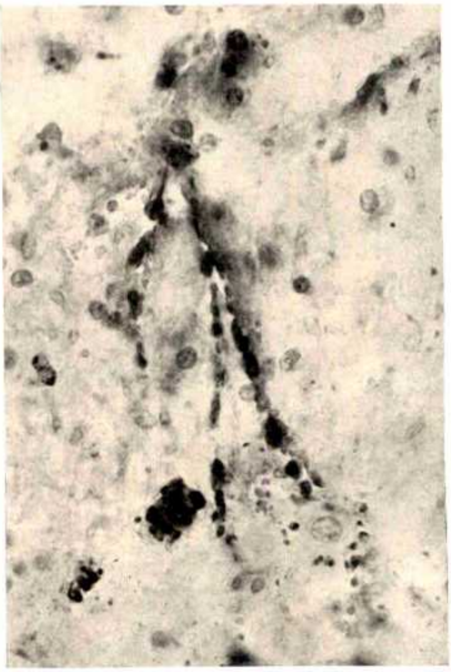

FIG. 4.

To illustrate paper by J. G. Greenfield and Lester S. King.

REFERENCES.

ARING, C. D. *Journ. Neurol. and Psychopath.*, 1937. In press.
BIELSCHOWSKY, M. *Neurol. Cent.*, 1904, **23**, 59, 770.
Idem. Journ. f. Psychol. u. Neurol., 1909, **14**, 131.
BODECHTAL, G., and GUTTMANN, E. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1931, **133**, 601.
Idem. Ibid., 1932, **138**, 544.
BOUMAN, L. "Diffuse Sclerosis (Encephalitis Periaxialis Diffusa)," 1934. John Wright & Sons, Ltd., Bristol.
DAWSON, J. W. *Trans. Roy. Soc. Edin.*, 1916, **50**, 517.
DOINIKOW, B. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1915, **27**, 151.
FARRAR, C. B. "Nissl und Alzheimer Arbeiten über die Grosshirnrinde," 1908. G. Fischer, Jena, **2**, 1.
GREENFIELD, J. G. *Journ. Neurol. and Psychopath.*, 1933, **13**, 289.
HASSIN, G. B. *Arch. Neurol. and Psychiat.*, 1936, **36**, 231.
HURST, E. W. *Brain*, 1925, **48**, 1.
JABUREK, L. *Arb. a. d. Neurol. Inst. Wien.*, 1931, **33**, 93.
JAKOB, A. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1914, **27**, 290.
Idem. "Normale und pathologische Anatomie und Histologie des Grosshirns," 1929. Deuticke, Leipzig u. Wien., Bd. 2.
KALTENBACH, H. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1922, **75**, 138.
KING, L. S. *Arch. Path.*, 1937. In press.
KING, L. S., and MEEHAN, M. C. *Arch. Neurol. and Psychiat.*, 1936, **36**, 547.
MARINESCO, G. *Ann. de Med.*, 1924, **16**, 5.
MARINESCO, G., and MINEA, J. *Rev. Neurol.*, 1909, **17**, 957.
Idem. Journ. f. Psychol. u. Neurol., 1910, **17**, 116.
MÜLLER, E. "Die Multiple Sklerose des Gehirns und Rucken-Marks," 1904. Jena.
PUTNAM, T. J. *Arch. Neurol. and Psychiat.*, 1936, **35**, 1289.
RAMON Y CAJAL, S. "Degeneration and Regeneration of the Nervous System," 1928. Oxford Univ. Press.
SCHOLZ, W. *Zeitschr. f. d. ges. Neurol. u. Psychiat.*, 1925, **99**, 651.
SIEMERLING, E., and RAECKE, J. *Arch. f. Psych.*, 1914, **53**, 385.
STRÄHUBER, A. *Ziegler's Beitr.*, 1903, **33**, 409.
Idem. Neurol. Cent., 1904, **23**, 55.
STRÜMPELL, A. *Ibid.*, 1896, **15**, 961.
TOYAMA, M. *Arb. a. d. neurol. Inst. Wien.*, 1931, **33**, 74.
WESTPHAL, A. *Neurol. Cent.*, 1918, **37**, 2, 407.

LEGENDS FOR ILLUSTRATIONS.

PLATE X.

FIG. 1.—A recent plaque, two to three months old, stained with hæmatoxylin and Scharlach R. The even distribution of lipoids throughout the tissue and the absence of special perivascular accumulations will be noted. The arrow points to rows of fat globules of the type shown in fig. 4 and described in the text. × 152.

FIG. 2.—The same field as fig. 1, but taken with polarized light to show the doubly refractile lipoids. × 152.

FIG. 3.—Cortical plaque, showing rod-shaped microglia laden with fat. Scharlach R with nuclear counterstain. × 513.

FIG. 4.—Rows of fat droplets interpreted (see text) as myelinated fibres which have not been phagocytized. Stained as above. × 513.

PLATE XI.

FIG. 5.—Mixed degeneration and regeneration of axis cylinders. The large "bomb" is a retraction ball, from which fine lateral fibrils are sprouting. Hortega double impregnation for neurofibrils. × 560.

FIG. 6.—Terminal loops, the type of regenerative phenomenon most frequent in plaques in cerebral white matter. Stain as in fig. 5. × 1200.

FIG. 7.—Degenerative swellings ("torpedoes") on the axones of Purkinje cells in a cerebellar plaque. Stain as in fig. 5. × 160.

FIG. 8.—Gliosis occurring within the same plaque illustrated in figs. 1 and 2. Victoria blue. × 255.

PLATE XII.

FIGS. 9 and 10.—Spindle cells described in the text. Hortega impregnation for connective tissue. Fig. 9, × 545; fig. 10, × 640.

FIGS. 11 and 12.—Active microglia, at the margin of the same plaque from which figs. 9 and 10 were taken, and stained by the identical method. × 500.

PLATE XI.

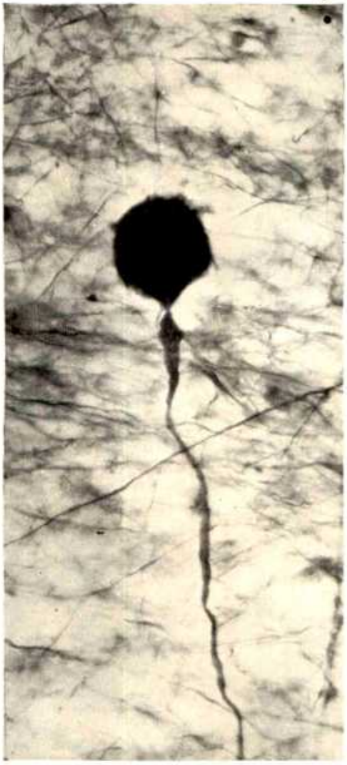

FIG. 5.

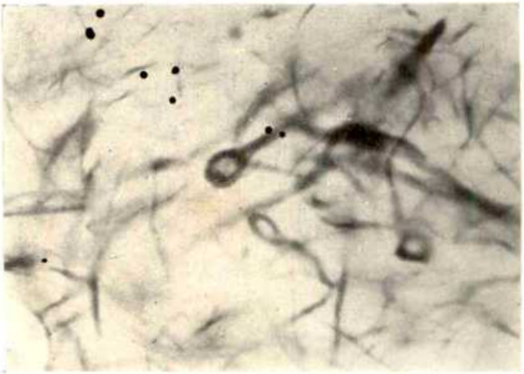

FIG. 6.

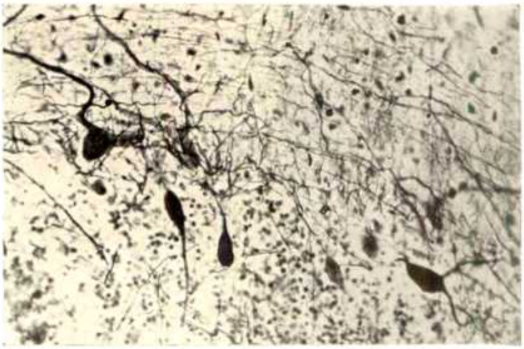

FIG. 7.

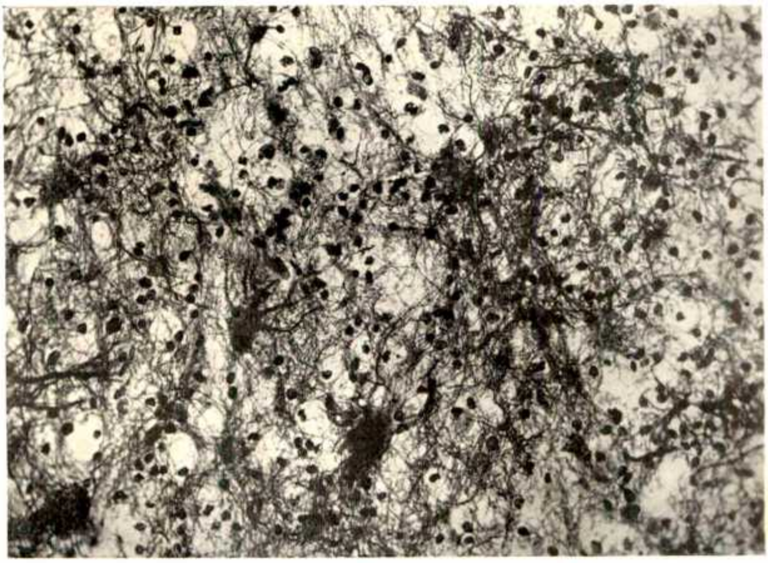

FIG. 8.

To illustrate paper by J. G. Greenfield and Lester S. King.

PLATE XII.

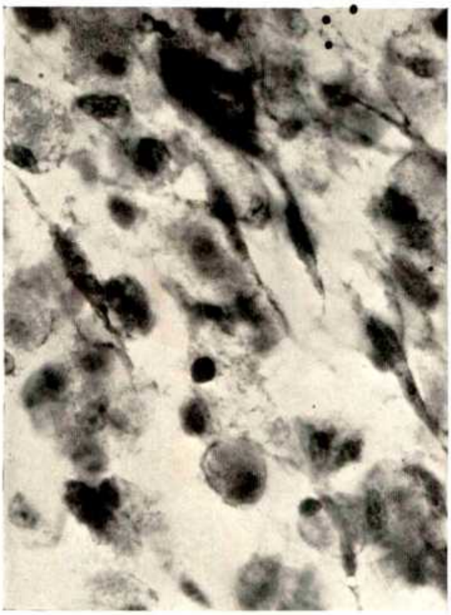

FIG. 9.

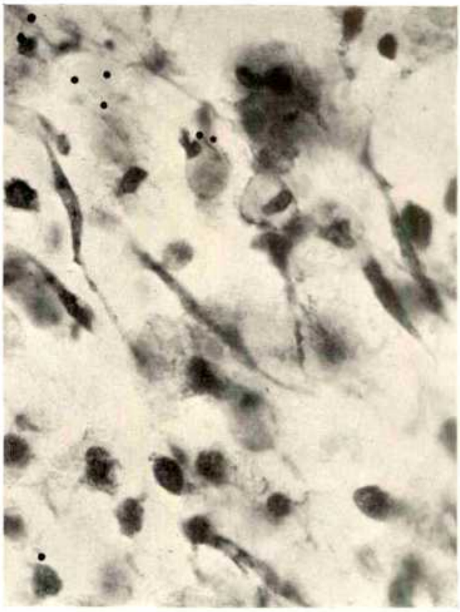

FIG. 10.

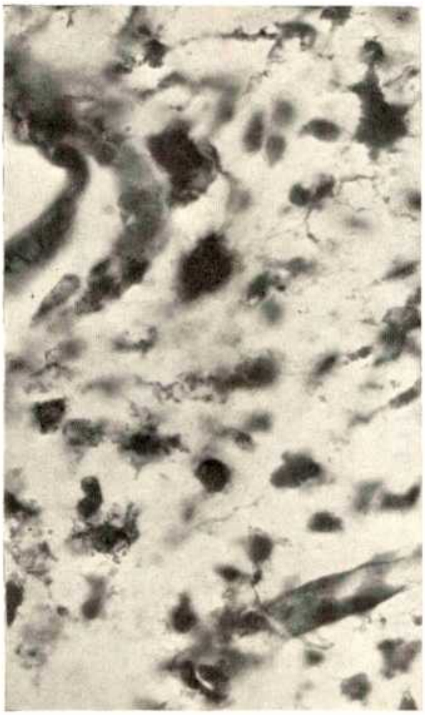

FIG. 11.

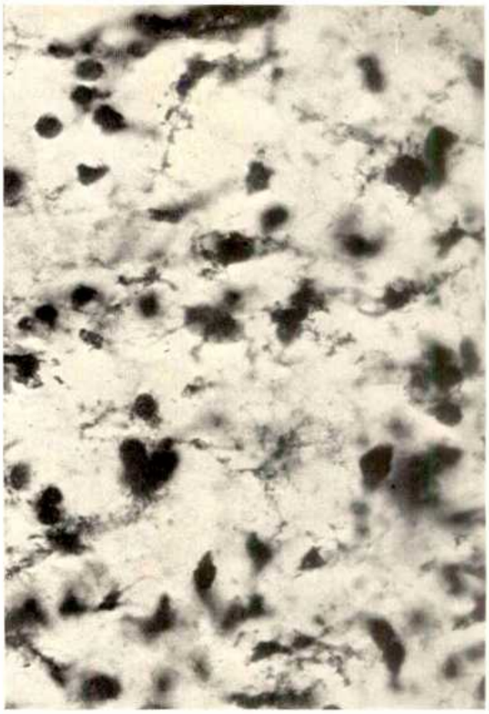

FIG. 12.

To illustrate paper by J. G. Greenfield and Lester S. King.

FURTHER STUDIES ON THE EFFECT OF HYPOTHALAMIC LESIONS UPON CARBOHYDRATE METABOLISM.[1]

BY DAVID CLEVELAND AND LOYAL DAVIS (CHICAGO).

IN a previous study [1] we have shown that properly placed lesions in the hypothalamus will ameliorate the symptoms of pancreatic diabetes and prevent the glycosuria and hyperglycæmia produced by stimulation of the superior cervical sympathetic ganglion. Further studies have revealed interesting information concerning the relation of the nervous system to carbohydrate metabolism.

Unipolar electrolytic lesions were made under asepetic conditions in the hypothalamus of cats and monkeys by means of the Horsley-Clarke stereotaxic apparatus. All of the animals were operated upon under sodium pentobarbitol anæsthesia (28 mg. per kilogram of body-weight). Standard measured diets of meat and milk were given before and after operation to all the cats, and standard diets of vegetables, fruits and milk to the monkeys. In some instances it was necessary to feed the animals by a stomach tube for short intervals with one egg in 80 c.c. of whole milk. Blood-sugar studies were made by the Randles-Grigg modification of the Folin-Wu technique on venous blood withdrawn approximately twenty to twenty-two hours after feeding. Glycosuria was estimated qualitatively and quantitatively by the Benedict test. One hundred and forty-seven cats and five monkeys were subjected to hypothalamic lesions. In each case the attempt was made to destroy the filiform nuclei, because our previous studies had shown that such lesions were most effective in carbohydrate metabolism regulation tests.

Blood-sugar curves immediately following lesions.—Fifty-seven cats had a transient elevation of the blood-sugar above 125 mg. per 100 c.c. of blood immediately post-operatively, which remained above normal over a period of three to twenty-seven days, with an average of 6·4 days. Four cats had a hyperglycæmia above 300 mg., the highest being 333 mg., but the average rise was to 158 mg. Three of the monkeys developed transient hyperglycæmia of 127, 142 and 134 mg. respectively, but in each case there was a return to normal levels on the fourth day. A fourth monkey had a low blood-sugar, which never rose to normal, following the production of a lesion in the hypothalamus.

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[1] From the Division of Surgery, North Western University Medical School.

Insulin sensitivity.—Fourteen cats with hypothalamic lesions were tested for insulin sensitivity by giving ½ unit of insulin per kilogram of body-weight intravenously. Five showed a marked and dangerous reaction to insulin and one cat died before intravenous glucose could be given (Chart 1). Seven were mildly to moderately sensitive to insulin, while two reacted in a normal manner.

Two of the monkeys with hypothalamic lesions had a marked and prolonged insulin reaction (Chart 1). A third monkey showed a marked hypoglycæmia, which returned to above normal within three hours. The fourth animal gave an entirely normal response.

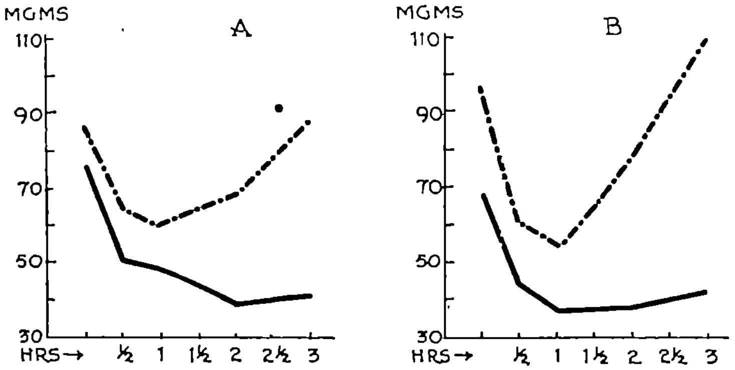

CHART 1.—Composite charts which show blood sugar levels after a hypothalamic lesion in comparison with normal animals after the injection of ½ unit of insulin per kilogram. A: Solid line represents the average reaction of five cats with such lesions; dotted line normal cats. B: Solid line represents two monkeys with such lesions: dotted line normal monkeys.

The cervical sympathetic trunk and superior cervical ganglion were removed on both sides in seven cats. Following this procedure the blood sugars remained at the lower limits of normal. Each animal showed a marked sensitivity to 0·5 unit of insulin and the blood-sugar did not return to normal until twenty-four or forty-eight hours after the injection. Three of the cats were subjected to a complete pancreatectomy and again were tested for insulin sensitivity on the following day. One died in a hypoglycæmia crisis after receiving 1·5 units, three times the amount of the test dosage. A second was saved by the administration of intravenous glucose solution, while the blood-sugar of the third did not drop materially. The latter two animals died on the fourth day of pancreatic diabetes. Two of the remaining four cats died of an upper respiratory tract infection. Hypothalamic lesions were made in the other two animals, and following this a pancreatectomy was performed. Both died of pancreatic diabetes. The lesion in each animal was poorly placed, leaving the filiform and periventricular nuclei intact.

Adrenalin reaction.—The adrenalin reaction was tested in thirteen cats and four monkeys with hypothalamic lesions and in four entirely normal cats, by injecting 0·1 c.c. of $\frac{1}{1000}$ adrenalin per kilogram of body-weight intramuscularly. Four of the cats with such lesions, which were very sensitive to insulin, showed a mild elevation of the blood-sugar ranging from 112 to 133 mg. (Chart 2); seven responded to rises to between 148 and 191 mg., and two had rises to 200 and 209 mg., respectively. One of the monkeys sensitive to insulin had a 20 mg. increase in the blood-sugar. The second monkey's blood sugar increased to 117 mg., while the remaining two animals had peaks of 176 and 181 mg. respectively. The responses in the four normal cats were all above 190 mg. In every instance, except in one monkey and one cat, the

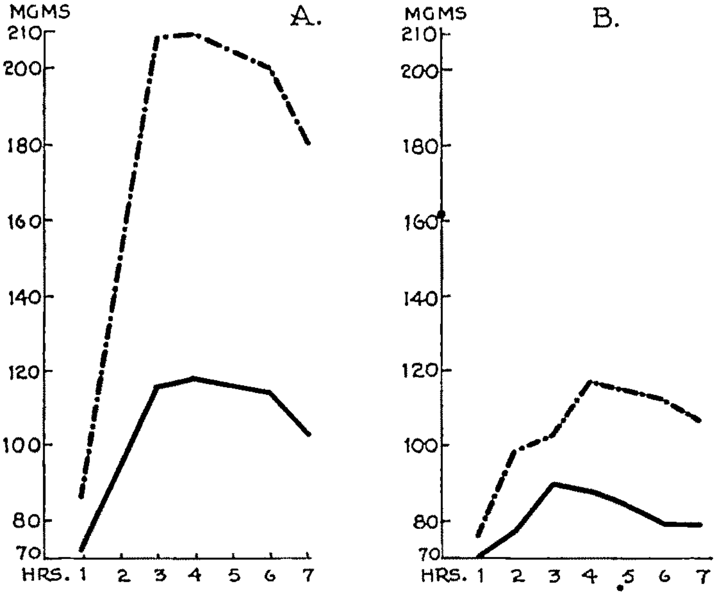

CHART 2.—Composite charts which show blood sugar levels of animals with hypothalamic lesions in comparison with normal animals after injection of 0·1 c.c., $\frac{1}{1000}$ adrenalin per kilogram. A: Solid line represents the average reaction of four cats with such lesions; dotted line four normal cats. B: Solid line represents the average reaction of two monkeys with such lesions; dotted line two normal monkeys.

blood-sugar was slightly elevated the following morning, but all had returned to or below the original level by the second day.

Anterior pituitary extract.—Thirteen cats and four monkeys with hypothalamic lesions, four cats with the spinal cord transected between the 5th and 7th cervical segments five days previously, and four normal cats were injected intraperitoneally daily with the equivalent of 3 grm. of anterior lobe in a saline extract (Schockaert method). All of the animals were injected over a period of nine days. Previous experiments had shown that an injection of 1 grm. daily was ineffective.

The four normal cats, two of the cats with hypothalamic lesions and one of the cats with a cervical cord section, developed a progressive rise in the blood-sugar to levels varying between 177 and 206 mg., and all showed a mild glycosuria. Seven cats with hypothalamic lesions, three cats with cervical cord sections, and two monkeys with hypothalamic lesions responded by a gradual elevation of the blood-sugar to levels between 123 and 163 mg., which, in comparison with the above group, shows a diminished response. There was a variation in both the urinary and blood-sugar from day to day in most of the animals, but on the average the peak occurred at the sixth day. Glycosuria was of a transient nature and was never more than very mild. The four insulin sensitive cats and two insulin sensitive monkeys (all with accurately placed hypothalamic lesions) developed a transient hyperglycæmia which never more than doubled the original level, and then gradually approached the normal. None of these animals showed any urinary reduction of Benedict's solution.

At a later period four sympathectomized cats (superior cervical ganglion and cervical trunk) responded to anterior lobe extract injections in a practically normal manner.

Ergotamine.—In order to determine the effect of ergotamine on the glycosuria and hyperglycæmia resulting from faradic stimulation of the superior cervical ganglion, experiments were performed on twelve female cats. Six were given subcutaneous injections of 0·5 mg. of ergotamine tartrate per kilogram of body weight. After the superior cervical sympathetic ganglion had been isolated from the rest of the field by a rubber dam, it was stimulated with a faradic current (Harvard inductorium with secondary coil at 8 cm. and one dry cell). Three stimuli of thirty seconds each were given in each experiment. Urine was collected before, during, and at fifteen-minute intervals for two hours after stimulation. Blood was collected one hour after the stimulation because previous experiments had shown that the hyperglycæmia was greatest at that time. Four of the cats showed no sugar in the urine, but one developed a moderate and one a heavy glycosuria (Chart 3). The four animals that did not develop glycosuria did not have a rise of blood-sugar of more than 35 mg. The other two cats had glycæmia responses to 227 and 258 mg.—a rise of more than 100 mg.

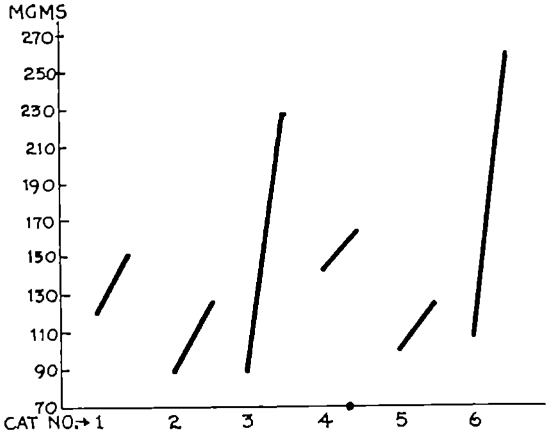

Chart 3.—Blood sugar levels resulting from faradic stimulation of superior cervical sympathetic ganglion in six cats injected with 0·5 mg. ergotamine tartrate per kilogram.

Four other animals were injected with 1·5 mg. of ergotamine per kilogram, following which stimulation of the superior cervical ganglion

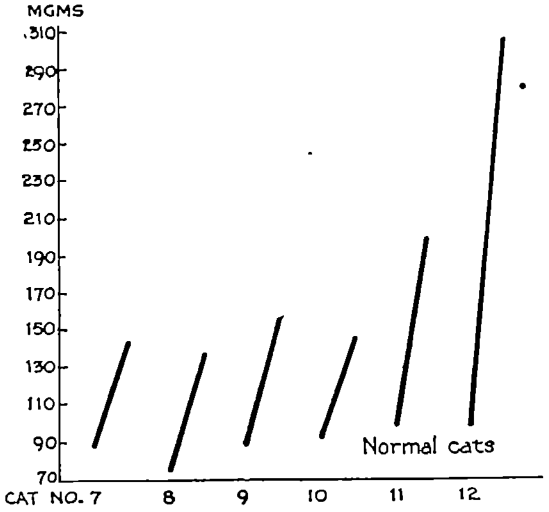

Chart 4.—Blood sugar levels resulting from faradic stimulation of superior cervical sympathetic ganglion in four cats injected with 1·5 mg. ergotamine tartrate per kilogram. Blood sugar levels of two normal cats after stimulation are shown for comparison.

was performed. The average blood-sugar rise was 59 mg., but in none did glycosuria develop. Hyperglycæmia and glycosuria developed promptly in two control animals under identical conditions (Chart 4).

Two of the cats from each experiment which did not develop a rise in blood-sugar were subjected to stimulation of the superior cervical ganglion two weeks later after all effects of the drug had disappeared and all responded in an entirely normal manner. As we have emphasized before, all animals must be well fed before this type of stimulation experiment is carried out.

COMMENT.—We have shown in a previous study that in cats and monkeys, properly placed lesions in the ventral part of the hypothalamus, involving the region in close proximity to the wall of the 3rd ventricle and particularly the filiform nuclei, have a definite effect upon carbohydrate metabolism. The amelioration of pancreatic diabetes, while more difficult to obtain than by hypophysectomy, seems fully as marked. The mechanism by which the hypothalamus participates in this function must as yet remain in doubt, or at least, a matter of conjecture. Lucke [2] has suggested than anterior lobe (contra-insular) hormones act on the hypothalamus by way of the cerebrospinal fluid. If this is so, injection of cerebrospinal fluid from a normal animal into a hypophysectomized-pancreatectomized animal would cause diabetic symptoms, whereas, in a hypothalamic lesion-pancreatectomized animal such an injection would have no effect.

It would appear that the mechanism of the hypothalamic lesion does not act by way of nerve tracts descending in the brain-stem and cervical cord, because animals with the cervical cord transected at the 6th cervical segment developed unmodified diabetes following pancreatectomy. It is believed by many, though it has not been proven, that connections exist between the filiform and medial hypothalamic nuclei and the hypophysis. Our experiments may offer some physiological evidence that this is true. Whether or not properly placed hypothalamic lesions ameliorate pancreatic diabetes by interruption of the nervous control of the hypophysis is by no means settled. The diminution of the effects of anterior lobe extracts by hypothalamic lesions may be due to interference by other factors in this complex mechanism.

SUMMARY.

1. Animals with experimental hypothalamic lesions usually have a hyperglycæmia immediately after operation, and then tend to have

glycæmic levels in the lower limits of normal and subnormal, if the lesions involve the medial and ventral hypothalamic area.

2. Destruction of the filiform, ventro-mesial, and perifornical nuclei and lesions of the ventricular wall produce increased and prolonged insulin sensitivity, diminished adrenalin response, diminished anterior lobe extracts response and amelioration of pancreatic diabetes.

3. Cervical sympathectomy does not ameliorate the symptoms of pancreatic diabetes in animals.

4. Transection of the cervical spinal cord between the 5th and 7th segments does not ameliorate pancreatic diabetes.

5. Ergotamine, if given in sufficiently large doses, prevents hyperglycæmia and glycosuria that otherwise results from stimulation of the superior cervical sympathetic ganglion.

BIBLIOGRAPHY.

[1] DAVIS, L., CLEVELAND, D., and INGRAM, W. R. "The Effect of Hypothalamic Lesions and Stimulation of the Autonomic Nervous System upon Carbohydrate Metabolism," *Arch. Neur. and Psych.*, 1935, **33**, 592.

[2] LUCKE, H., and HAHNDEL, H. "Untersuchungen über den Wirkungsmechanismus des kontrainsularen Hormons des Hypophysenvorderlappens: VI. Die Möglichkeit eines biologischen Nachweis des kontrainsularen Hormons im Liquor cerebrospinalis." *Ztschr. f. d. ges. exper. Med.*, 1933, **91**, 704.

VESTIBULAR PHENOMENA OF CENTRAL ORIGIN.[1]

(AN EXPERIMENTAL STUDY IN *Macacus Rhesus*.)

BY ARMANDO FERRARO, S. E. BARRERA AND GEORGE A. BLAKESLEE.

(From the Department of Neuropathology, New York State Psychiatric Institute and Hospital, New York, N.Y.)

I.—INTRODUCTION.

Previous observations reported from this laboratory and many likewise reported from other laboratories have established a group of symptoms which may be considered as characteristic of vestibular lesions in experimental animals.

The first paper from this laboratory dealing with the effects of lesions of the labyrinth and of the 8th nerve in *Macacus rhesus* [1] reported a group of symptoms which may be considered as typical of unilateral peripheral vestibular lesions. These symptoms include, in the acute stage, falling toward the side of the lesion; postural asymmetries, including torsion of the chin towards the opposite side, flexion of the occiput on the ipsilateral shoulder and relative flexion of the ipsilateral limbs; nystagmus toward the opposite side (quick component); ipsilateral deviation and tendency to spiral around the long axis of the body toward the side of the lesion in climbing a straight pole, swimming under water and jumping through the air. In addition a variable degree of ipsilateral hypotonia and diminution of the deep reflexes may be present. These findings are in accord with those presented for various animals by many authors, and agree essentially with those observed after unilateral labyrinthectomy in the monkey by Magnus [2].

The acute symptoms enumerated above vary considerably in severity from animal to animal, especially with regard to the postural asymmetries, particularly of the head, where degrees of torsion of the chin to the opposite side may vary from 5 or 10 degrees to perhaps 45 degrees from the vertical. The tonic and reflex difference likewise may vary considerably from animal to animal. The most characteristic and most constant findings, aside from the torsion of the head, are the nystagmus and the asymmetries in motion typified by the tendency to spiral around the long axis on climbing, swimming or jumping. In the typical peripheral lesion the nystagmus may be rather short-lived, lasting perhaps twenty-four hours. In the chronic stage the animal may show postural asymmetries of the head and the asymmetries of motion enumerated above as the only definite findings. These findings seem to us to be characteristic of peripheral lesions known to be vestibular in type and they may thus be considered as typical of vestibular dysfunction.

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[1] Read by title at the meeting of the American Neurological Association, June 1, 1936.

In a second paper entitled, "The Effects of Lesions of the Juxta-restiform Body (I.A.K. Bundle) in *Macacus rhesus* Monkeys" [3] reference was made to the effects of lesions involving essentially the large region describable topographically as the intra-medullary portion of the juxta-restiform system, or more properly known as the lateral or descending portion of the vestibular nuclear complex. Symptoms the same in type as those due to peripheral lesions but much more severe in degree were found to be associated with large lesions of this portion of the central vestibular mechanism. The postural asymmetries, including the torsion of the head and particularly the asymmetries of the limbs, were more marked. The nystagmus was more active and lasted for a longer period. The same asymmetries of motion were present but were more marked and at times in locomotion on the floor amounted even to rolling movements. No ataxia or dysmetria could be found in typical cases. The symptoms, in addition to being more severe in the acute stage following the operation, persisted for a much longer period and could be seen definitely even after survival periods of several months.

In light of the obviously greater severity of symptoms associated with large central vestibular lesions as compared to those due to peripheral vestibular lesions the point arose as to whether other afferent components besides those from the labyrinths are involved in the central vestibular response. For this reason it seemed justified to proceed a little further and investigate the effects of central vestibular lesions in the absence of peripheral vestibular receptors. A similar investigation was undertaken by Spiegel and Sato [4], who, in 1926, studied dogs in which unilateral vestibular nuclear lesions were produced associated with bilateral section of the 8th nerves. In their animals the experiments were acute, the bilateral nerve section and the vestibular nuclear lesion being performed at the same time. These authors found that in the dog many of the elements associated with large vestibular nuclear lesions can be reproduced, even in the absence of peripheral stimuli by way of the 8th nerves. We considered it interesting and important to extend these observations to monkeys and to study the effects of such combined lesions even in animals in which the labyrinths or nerves had been destroyed at considerable periods of time before the vestibular nuclear lesion.

II.—PROCEDURE.

Macacus rhesus monkeys were used throughout the experiments. They weighed on the average from 8 to 10 lb. and the vestibular function was tested clinically before operation by the rotation, caloric and galvanic tests. Labyrinthectomy was performed in the manner described by Northington and Barrera, using essentially the Hinzberg approach. Section of the nerve was performed in the usual manner with a sub-occipital approach and upward and medial retraction of the cerebellar lobe. These operations could be performed practically bloodlessly under ether anæsthesia and the animals could be observed usually at an interval of one to two hours after they left the operating table. At that time they were usually active and manifested the typical symptoms of the acute phase. The central vestibular lesions were made by using a sub-occipital approach with gentle upward retraction of the vermis and lateral lobes of the cerebellum. In this way a clear view of the ventricular floor and lateral wall of the ventricle could be usually obtained and the lesion could be placed at any desired point. In the present paper we shall not be concerned with the variations in the effects of central lesions depending upon whether the lesion is placed in the medial or lateral nuclear groups of the vestibular complex, or whether it is more caudally or cephalically placed. We shall be concerned here essentially with the effects of large diffuse central vestibular lesions involving a major portion of the central vestibular complex, which produced typical unilateral vestibular signs of marked degree similar to those reported in our paper of last year on the effects of lesions of the intra-medullary portion of the juxta-restiform system.

Further lesions used in the experiment included section of the dorsal cervical roots, which was performed by making a simple cervical laminectomy and then sectioning the dorsal roots within the dura as they entered the cord. Section of the supra-medullary portion of the juxta-restiform system was performed by making a cut in the lateral wall of the ventricle at an angle of approximately 45 degrees to the horizontal.

The only other operative procedure used was removal of the motor area. This was easily performed after it had been outlined by electrical stimulation with the Harvard inductorium.

The animals were observed carefully for all of the typical neurological symptoms, and moving pictures were made to demonstrate the typical abnormal features. After varying periods of time the animals were sacrificed and their nervous systems stained either by the Marchi, Weigert or Nissl methods. The temporal bones were removed in most cases and serial sections stained by hæmetoxylin and eosin. In all, over twenty-five monkeys have been used up to date for this experiment. In addition to these many monkeys have been used for studying the effects of various small lesions placed at different points in the vestibular nuclear complex. The latter, with the detailed anatomical studies associated with the vestibular nuclear lesions, will be reported at length elsewhere.

III.—Observations.

A. *Unilateral labyrinthectomy followed by section of the ipsilateral 8th nerve.*—Table I summarizes the typical findings associated with

TABLE I.

A.—Phenomena produced by a unilateral labyrinthectomy.	*B.—Changes following subsequent ipsilateral 8th nerve section.*
1. Falling—to side of lesion.	
2. Asymmetries in posture.	
(*a*) Head—chin to contralateral side.	None.
(*b*) Relative slight ipsilateral limb flexion and	
(*c*) Relative slight contralateral limb extension.	
(*a*), (*b*) and (*c*) show considerable individual variation.	
3. Spontaneous nystagmus—to opposite side (quick component). Average duration approximately 24 hours.	*Note.*—If 8th nerve section alone is performed the phenomena are the same as in *A*.
4. Asymmetries in movement	
(*a*) Jumping—spiralling around long axis to same side.	
(*b*) Swimming—spiralling around long axis to same side.	
(*c*) Climbing single pole—spiralling around long axis to same side.	
5. Ipsilateral hypotonia—considerable individual variation.	
6. Ipsilateral hyporeflexia—marked individual variation.	
7. No rolling movements.	
8. Absence of ataxia or dysmetria.	
9. Disabilities vary considerably in degree. Slight asymmetrical head posture and asymmetries in motion persist indefinitely.	

unilateral labyrinthectomy as reported in an earlier communication. In these cases the labyrinth was proved to be inactive to caloric testing by which no response was obtained from the labyrinthectomized side on the introduction of cold water into the external auditory meatus. Neither the rotation tests nor the galvanic tests were of much significance in the unilateral labyrinthectomized case, because the rotation test may be significant only in the acute phase and the galvanic test may be of significance only if the labyrinthectomy happens to result in degeneration of the nerve.

TABLE II.

A.—Phenomena produced by unilateral labyrinthectomy or 8th nerve section.	*B.—Phenomena following subsequent large ipsilateral vestibular nuclear lesion.*
1. Falling—to side of lesion.	1. Falling—to side of lesion more marked than in *A*.
2. Asymmetries in posture	2. Asymmetries in posture.
(*a*) Head—chin to contralateral side.	(*a*) Head—marked torsion of chin to opposite side.
(*b*) Relative slight ipsilateral limb flexion, and	(*b*) Relative ipsilateral limb flexion.
(*c*) Relative slight contralateral limb extension.	(*c*) Relative contralateral limb flexion.
(*a*), (*b*), and (*c*) show considerable individual variation.	(*a*), (*b*), and (*c*) all much more marked than 2 (*a*), 2 (*b*), and 2 (*c*) in *A* with very little individual variation.
3. Spontaneous nystagmus — to opposite side (quick component). Average duration approximately 24 hours.	3. Spontaneous nystagmus — marked, to opposite side predominantly. Duration much longer than in *A*.
4. Asymmetries in movement.	4. Asymmetries in movement.
(*a*) Jumping—spiralling around long axis to same side.	(*a*) Jumping—spiralling around long axis to same side.
(*b*) Swimming—spiralling around long axis to same side.	(*b*) Swimming—spiralling around long axis to same side.
(*c*) Climbing single pole — spiralling around long axis to same side.	(*c*) Climbing pole—spiralling around long axis to same side.
5. Ipsilateral hypotonia—considerable individual variation.	5. Ipsilateral hypotonia—variable.
6. Ipsilateral hyporeflexia—marked individual variation.	6. Ipsilateral hyporeflexia—variable.
7. No rolling movements.	7. Occasionally rolling movements around long axis to side of lesion in very acute stage. More marked if any cerebellar complication present.
8. Absence of ataxia or dysmetria.	8. Absence of ataxia or dysmetria.
9. Disabilities vary considerably in degree. Slight asymmetrical head posture and asymmetries in motion persist indefinitely.	9. Disabilities severe in degree. Asymmetries in posture and in motion may persist indefinitely.

Section of the 8th nerve intracranially subsequent to an earlier labyrinthectomy on the same side produced no additional symptoms nor an increase in the existing symptoms, provided that the labyrinthectomy was found by functional testing to have been successful.

B. *Unilateral labyrinthectomy or section of the 8th nerve followed by an ipsilateral large vestibular nuclear lesion.*—Table II presents comparative tables showing the increase in vestibular symptoms associated with the central nuclear lesion as compared to those existing as a result of the previous lesion of nerve or labyrinth on the same side. This increase could be noted if the second operation were performed in the relatively acute phase following the first operation, or if it were performed at a considerable time afterward. As can be seen from the table the nystagmus, while in the same direction, was more active and of longer duration in the case with a central lesion than in the peripheral case. The postural asymmetries became more marked in the sense that the chin was twisted very sharply towards the opposite side and the limbs showed greater flexion of the ipsilateral as compared to the contralateral limbs. The asymmetries in movement were likewise greater; the tendency toward rolling movements and spiralling around the long axis of the body toward the side of the lesion were much more marked in the case of the large central lesion. All of the symptoms in the case of the central lesion persisted at a greater intensity and for a longer period of time than was found in any typical case of unilateral peripheral lesion involving either labyrinthectomy or section of the 8th nerve.

All of these findings would seem to indicate that other elements, in addition to the components from the vestibular end organ of the same side, play upon the central vestibular mechanism; otherwise one might expect that symptoms due to lesions of the nuclei would be the same as those associated with lesions of the nerve or labyrinth of the same side. Such is not the case, however. Magnus and others have mentioned the possibility of the normal ear playing some role in the symptoms following unilateral ear or nerve lesions, and for this reason the following crucial experiment was undertaken.

C. *Bilateral labyrinthectomy followed by unilateral lesion of the central vestibular nuclei.*—Table III summarizes the effects of bilateral labyrinthectomy in the monkey, as compared to bilateral labyrinthectomy followed by a large unilateral vestibular nuclear lesion. The most important feature in these cases is that a large unilateral vestibular nuclear lesion subsequent to a bilateral labyrinthectomy, or even bilateral section of the 8th nerve, produced definite unilateral symptoms which, in light of our earlier papers and unpublished experiments, we believe are definitely vestibular in type.

These effects differed in fact very little either in degree or in type from those associated with similar vestibular nuclear lesions in the presence of intact labyrinths or nerves. The only difference seemed to be that in the presence of previous bilateral lesions of labyrinths or nerves there was some evidence of bilaterality in the symptoms as manifested by some abductive postures of the limbs contralateral to the vestibular nuclear lesion and by more bilateral unsteadiness. The most interesting feature, however, was that even in the presence of degenerated nerves on both sides, typical unilateral vestibular symptoms occurred. The nystagmus in most of these cases was active and typical of unilateral vestibular nuclear lesions. Its direction was to the opposite side. Its duration, varying from animal to animal, was from a few days after operation to a period of even six weeks in one case, at the end of which time a conjugate deviation of the eyes occurred. The postural asymmetries were definite. The chin was twisted sharply toward the opposite side, the occiput was flexed on the ipsilateral shoulder, there were rather marked but variable relative ipsilateral flexion of the limbs and contra-

TABLE III.

A.—Phenomena resulting from bilateral labyrinthectomy (one stage).	*B.—Phenomena resulting from a large unilateral vestibular nuclear lesion, subsequent to A.*
1. Falling—to either side or, if looking upward, occasionally backwards.	1. Falling—predominantly to side of nuclear lesion.
2. Asymmetries in posture.	2. Asymmetries in posture.
(*a*) Head—may show dorsiflexion, chin in midline.	(*a*) Head—chin twisted to opposite side.
(*b*) No asymmetry. Both sides alike.	(*b*) Relative ipsilateral limb flexion.
(*c*) No asymmetry. Both sides alike.	(*c*) Relative contralateral limb extension.
3. Spontaneous nystagmus—none. No nystagmus induceable by rotation or caloric testings.	3. Spontaneous nystagmus—to side opposite nuclear lesion (quick component).
4. Asymmetries in movement.	4. Asymmetries in movement.
(*a*) Jumping—may do back flips.	(*a*) Jumping—rarely performed. If done spiralling backward and around long axis to side of nuclear lesion occurs.
(*b*) Complete disorientation, if head under water would drown.	(*b*) Swimming—general disorientation with spiralling under water around long axis to side of nuclear lesion.
(*c*) Climbing pole—disoriented in space, bizarre positions (head down, &c.).	(*c*) Climbing pole—spiralling around long axis to side of nuclear lesion.
5. No definite hypotonia.	5. A variable degree of ipsilateral hypotonia.
6. No definite hyporeflexia.	6. A variable degree of ipsilateral hyporeflexia.
7. No rolling movements around long axis.	7. Occasionally rolling movements around long axis to side of nuclear lesion. Especially so if any cerebellar complication is present.
8. Absence of ataxia or dysmetria.	8. Absence of ataxia or dysmetria.
9. Phenomena are severe and tend to be long lasting. A certain degree of recovery seems to occur.	9. Phenomena are severe and tend to be long lasting. The postural asymmetries may last indefinitely.

lateral extension, and the animal showed definite asymmetry in movements in the sense of a tendency to spiral around its long axis toward the side of the central lesion on jumping or climbing, and even mild rolling movements in the early stage occurred in one case. In most of the cases studied so far the symptoms were long lasting. The asymmetry of the head in some of the cases has manifested a torsion of the chin at perhaps a plane of 60 degrees from the vertical, lasting for even six weeks. No tremors of any type have been noted to date in these animals. The lesions of the ear and nerve were found, before the second operation, to be effective, for no responses could be obtained by caloric testing in either the labyrinthectomized or neurectomized animals, and in addition no response could be obtained by galvanic testing in the animals with section of the nerves. The time at which the central lesions was performed relative to the first operation did not seem to influence the results. In one case the second operation was performed six months after the first operation, and in other cases periods as short as two weeks were allowed to elapse before the second operations were performed. No essential differences in the intensity of the symptoms referable to the second operation occurred.

TABLE IV.

Phenomena following unilateral lesions of the supramedullary portion of the juxta-restiform system.

1. Falling—occasional, to side opposite the lesion.
2. Asymmetries in posture.
    (a) Head—usually normal but occasionally shows slight twist of chin towards ipsilateral side.
    (b) (c) Body and limb posture normal.
3. Spontaneous nystagmus—to side of lesion.
4. Ipsilateral hypotonia (slight and inconstant).
5. Ipsilateral hyporeflexia (slight and inconstant).
6. Absence of rolling movements.
7. Climbing—spiralling around long axis to opposite side.
8. Jumping—spiralling around long axis to opposite side.
9. Swimming—essentially normal.
10. Absence of definite ataxia or dysmetria in purest cases.
11. Relative slight degree of disabilities as compared to those following lesions of *A*; tendency to disappear rather rapidly.

This is the basic experiment from which the additional experiments have been devised. It proved that typical vestibular symptoms can be elicited from a unilateral lesion in the monkey even in the absence of impulses or components from the labyrinths. It confirmed in the monkey the earlier observations of Spiegel and Sato made in the dog. It raised the question as to what other components may enter into the vestibular nuclear complex and thus account for some of the vestibular elements in the symptoms which were elicitable by the second operation. One group was the fibres from the cerebellum by way of the supramedullary portion of the juxta-restiform system. That these fibres were associated with vestibular functions was found in our experiment in which, upon sectioning of these fibres, we found symptoms which appeared to us to be definitely vestibular in type but opposite in direction and less in degree than those associated with lesions of the underlying vestibular nuclear complex. Table IV shows these symptoms. In studying this group of fibres the following experiment was performed.

TABLE V.

A.—Phenomena resulting from bilateral labyrinthectomy (one stage).	*B.—Phenomena occurring following subsequent section of supermedullary portion of the juxta-restiform position.*
1. Falling—to either side or, if looking upwards, occasionally backwards.	1. Falling—predominantly to side opposite fibre lesion.
2. Asymmetries in posture.	2. Asymmetries in posture.
(*a*) Head—may show dorsiflexion, chin in midline.	(*a*) Head—may show slight twist toward side of central lesion.
(*b*) No asymmetry. Both sides alike.	(*b*) Usually normal.
(*c*) No asymmetry. Both sides alike.	(*c*) Usually normal.
3. Spontaneous nystagmus — none. No nystagmus inducible by rotation or caloric testings.	3. Spontaneous nystagmus—to side of lesion (quick component).
4. Asymmetries in movement.	4. Asymmetries in movement.
(*a*) Jumping—may do back flips	(*a*) Jumping—spiralling around long axis to side opposite lesion. When jumping usually shows back flips and spiralling combinations.
(*b*) Complete disorientation, if head under water would drown.	(*b*) Swimming—general disorientation under water. No predominant movement seen.
(*c*) Climbing pole—disoriented in space, bizarre positions (head down, &c.).	(*c*) Climbing pole—may be generally disoriented with bizarre postures but predominant spirally around long axis towards side opposite central lesion.
5. No definite hypotonia.	5. Occasionally slight relative ipsilateral hypotonia.
6. No definite hyporeflexia.	6. Occasionally slight relative ipsilateral hyporeflexia.
7. No rolling movements around long axis.	7. No rolling movements.
8. Absence of ataxia or dysmetria.	8. Absence of ataxia or dysmetria.
9. Phenomena are severe and tend to be long lasting. A certain degree of recovery seems to occur.	9. Phenomena in addition to those in *A* tend to be transient except for some asymmetries in movement which may remain indefinitely.

D. *Bilateral labyrinthectomy followed by unilateral section of the supra-medullary portion of the juxta-restiform system.*—In these animals the symptoms which we reported last year as typical of unilateral section of the supra-medullary portion of the juxta-restiform fibres occurred. These included nystagmus toward the same side, slight torsion of the chin toward the same side, tendency to fall toward the opposite side, and tendency to spiral around the long axis toward the opposite side on jumping or climbing. The symptoms appeared to be the same in intensity in these cases as those associated with lesions of the juxtarestiform system in otherwise intact animals. Bilateral labyrinthectomy did not prevent the development of these symptoms. Table V shows these results.

Another possible component is that from the dorsal roots. To study this the following experiments were performed.

E. *Unilateral labyrinthectomy followed by ipsilateral section of the dorsal cervical roots, and the same operations performed in the reverse order.* In these operations the element of the vestibular symptoms which was studied was the rotated posture of the head. In typical unilateral ear cases the chin was turned toward the opposite side. If, in the presence of such a twist, the ipsilateral 2nd, 3rd and 4th dorsal cervical roots were sectioned intradurally there occurred either a neutralization or, as in most cases, even a reversal of the twist so that the chin came to point either vertically downward or toward the side of the ear and root lesions. If the dorsal roots of one side were cut the chin pointed slightly toward the side of the sectioned roots. In some cases no twist occurred, but in the majority a deviation of perhaps 10 degrees from the vertical was found. This was reversible by subsequent labyrinthectomy on the same side, and the degree of twist found as a result of the labyrinthectomy was about the same as that which resulted from labyrinthectomy in an otherwise intact animal. This experiment would seem to show that at least two components, one from the labyrinth and one from the dorsal roots, are involved in the posture of the head. This was commented upon in the earlier paper of Northington and Barrera.

F. *Bilateral section of the dorsal roots followed by unilateral labyrinthectomy.*—Three operations of this type have been performed to date. In two of them no torsion of the chin toward the opposite side occurred following unilateral labyrinthectomy. In the third case some torsion of the chin occurred toward the side of the intact labyrinth.

G. *Bilateral section of the dorsal cervical roots associated with unilateral vestibular nuclear lesions.*—In two cases bilateral section of the dorsal cervical roots, and at the same time a unilateral vestibular nuclear lesion were performed. So far as the posture of the head was concerned there was no difference between these animals and other animals in which unilateral vestibular nuclear lesions were performed in otherwise intact animals. The typical results of large unilateral vestibular nuclear lesions appeared.

In light of the reports of Henri [5], Aronovitch and Pike [6], and Wilson and Pike [7] on the importance of cerebral components on the vestibular symptoms, experiments have been and are being performed on the relation of lesions of the motor area of the cortex to the symptoms due to vestibular dysfunction. These will be reported at a later date.

IV.—Discussion.

Northington [8] reported a case of involvement of the vestibular nuclear complex of one side by an abscess in which the patient showed typical symptoms characteristic of sudden loss of peripheral vestibular function on that side, despite the fact that the patient apparently had had a dead labyrinth on that side for two years. So far as we are aware no adequate experimentation has been made to date to account for such cases and other similar cases. Dohlman [9], working on rabbits, found that after as complete remission of symptoms as would occur following unilateral labyrinthectomy, subsequent section of the 8th nerve on the same side produced a return of the typical, acute, unilateral vestibular signs. He concluded that impulses from Scarpa's ganglion were constantly entering the central nervous system through the 8th nerve independent of any impulses from the end organs in the ear. Thus a relative degree of vestibular function could be maintained even in the absence of the labyrinth itself. We have failed to note any change in the symptoms in the monkey when the 8th nerve of one side was cut subsequent to labyrinthectomy on that side.

Considerable variation exists from animal to animal with regard to the intensity of the symptoms associated with unilateral labyrinthectomy. The question might be raised as to whether this is due to involvement of Scarpa's ganglion in some cases and not in others, in line with the hypothesis of the importance of the ganglion expressed by Dohlman. Magnus also noted the great variation from animal to animal in the symptoms associated with unilateral labyrinthectomy, and claimed that the symptoms tended to be less in degree the more carefully the operation was performed. In our large series of unilateral monkeys we found variations of perhaps 10 to 40 degrees in the angle of twist of the head and the additional symptoms have always been definitely detectable. So far we have not been able to correlate the variations in the head posture with involvement of Scarpa's ganglion. The ganglion in the monkey is located practically at the internal auditory meatus and may be involved in some cases of labyrinthectomy and not in others. In some cases the labyrinthectomy may be done with relatively complete sparing of the ganglion. In such cases, despite a non-functioning labyrinth as detected by the caloric test, the nerve is not degenerated. In other cases the labyrinthectomy extends deeply enough to damage or destroy the ganglion with subsequent degeneration of the nerve. Both classes show similar variations in a large group of operations, and there is no correlation between the degree of head torsion and the involvement or sparing of the ganglion. It seems as if there may be basic differences between animals in the functional importance of similar cell or fibre groups and thus that there may be room for considerable variation in the responses of various animals to the destruction of these groups.

It seems to us that the present work in the monkey and the earlier work of Spiegel and Sato in the dog, especially the basic experiments in which unilateral vestibular nuclear lesions were performed subsequent to bilateral labyrinthectomy, supply an explanation for the possibility of unilateral vestibular signs following loss of labyrinthine or nerve function on the same side as reported by Northington. This might simply mean that clinically an involvement of the associated vestibular nuclear complex may exist independently of the labyrinth or nerve and be responsible for the symptoms. These experiments have shown beyond a doubt that this is the case inasmuch as typical unilateral vestibular signs can occur even in the absence of functioning labyrinths or 8th nerves. The case in our material most resembling the clinical occurrence is that in which a unilateral vestibular nuclear lesion was performed following the ipsilateral labyrinthectomy or section of the nerve. In this case typical unilateral vestibular symptoms occurred subsequent to the nuclear lesion even though considerable recovery had occurred following the initial operation.

The question arose as to why in such cases the symptoms associated with the nuclear lesion were more pronounced than those associated with the lesion of nerve or labyrinth. The suggestions developed that perhaps the representation of the nuclei was bilateral, or that other afferent impulses or components enter the vestibular nuclear complex enabling it to carry on a vestibular function in addition to that mediated through it from the vestibular organs themselves. The probability of additional afferent components become even greater in light of the basic experiment in which unilateral vestibular nuclear lesions were performed subsequent to bilateral labyrinthectomy or bilateral section of the nerves. In these experiments the possibility of vestibular components from the second end organ was eliminated and the symptoms resulting from the second operation must be due to involvement of other components than those from the vestibular end organs.

No single element in the typical vestibular syndrome failed to appear in the operation involving the nuclei subsequent to bilateral vestibular peripheral loss. The typical nystagmus to the opposite side occurred. The postural asymmetries and the motor asymmetries which appeared following this operation were in degree definitely comparable to those seen in similar unilateral vestibular nuclear lesions in otherwise intact animals. This would mean that the other afferent components playing a part in the vestibular responses are all represented in the nuclear complex responsible for the so-called vestibular manifestations.

The nature of the other afferents which it seems necessary to assume in light of the experiments still remains obscure.

The first and probably best known anatomical components entering the vestibular complex in addition to those from the vestibular nerve comprise the fibres which enter the vestibular nuclei through the juxtarestiform system, mainly through the large myelinated fibres which lie medial to the superior cerebellar peduncle, apparently connecting the roof nuclei of the cerebellum with the vestibular nuclear complex. That there is a " vestibular " function associated with these fibres can be seen from the work which we reported last year in which, after section of these fibres of one side we found symptoms such as nystagmus, falling to one side, asymmetrical posture of the head and asymmetries of movement, which were the same in type as those associated with unilateral vestibular nerve or nuclear lesions, but were much less in degree and were opposite in direction. The section of these juxtarestiform fibres in an animal in which both labyrinths had been previously removed produced symptoms identical to those which one would expect from section of these fibres in otherwise normal monkeys. Typical "vestibular" symptoms occurred with slight twist of the head and nystagmus toward the side of the lesion. This would seem to indicate that the fibres in question do to some extent carry into the central vestibular complex stimuli apparently independent of the vestibular peripheral system. These stimuli may originate from the cerebellum. This type of experiment proves conclusively the contention that interference with stimuli other than those originating in the peripheral vestibular apparatus may be responsible for the reappearance of vestibular symptoms in the absence of the peripheral vestibular apparatus.

There is also the possibility of components from the dorsal roots, section of which had been considered of importance in the work of Magnus and in some of our previous work. We have been able to demonstrate again that unilateral section of dorsal cervical roots associated with unilateral labyrinthectomy produces definite modifications of the labyrinthine effect. It seems that dorsal roots undoubtedly play some part with regard to the posture of the head seen in unilaterally labyrinthectomized monkeys, and the effect does not seem to be fixed when the lesion of the roots is bilateral. In some of our animals we were able to confirm the earlier work of Magnus with regard to the failure of development of some of the postural asymmetries, especially that of the head, when the labyrinth was removed subsequent to a section of both sets of dorsal cervical roots. In one of our cases, however, the usual typical asymmetrical posture of the head developed following unilateral labyrinthectomy even though the 2nd, 3rd and 4th posterior cervical roots had been cut on both sides previously. We have not been able to account for these variations except on the basis of the possibility that the various physiological components play roles of varying degrees of importance in different animals.

The section of the dorsal roots does not, however, modify to an appreciable extent the effect of subsequent unilateral vestibular nuclear lesions. In cases where the roots had been previously cut on both sides the typical marked asymmetrical picture of the head resulted when the nuclear lesion was performed. It may be interesting to note that section of both sets of roots associated with either the unilateral labyrinthectomy or unilateral vestibular nuclear lesion produces a much greater general disability in the general behaviour of the animal than does the labyrinthectomy, root lesion, or nuclear lesion alone.

So far as we are aware no conclusive proof has been given of the anatomical existence of myelinated fibres connecting the dorsal roots or their nuclei with the vestibular nuclear complex. In our animals with section of various dorsal roots [10] and of lesions of the dorsal columns [11] and dorsal column nuclei [12] we have not been able to find by the Marchi method any degenerating fibres entering the vestibular nuclear complex. Ranson [13] and his co-workers and Sherrington [14] in their studies of the distribution of the upper dorsal and cervical roots, respectively in the cat and monkey, likewise failed to report any degenerating fibres to the vestibular nuclear complex. In our cases involving section of the dorsal spino-cerebellar tract and restiform body [15] we have likewise been unable so far to detect degenerating fibres going into the vestibular nuclear complex. The fact that studies to date have failed to reveal myelinated fibres entering the vestibular nuclear complex does not of course mean that many short and perhaps unmyelinated fibres are not present. This may possibly be the case.

The effects of associated lesions of area 4, or the stimulatable contralateral motor area, on the symptoms produced by unilateral labyrinthectomy remain undecided at the present time, but our impression is that they are not very marked.

A more detailed investigation of this source of impulses or of other likely sources of components from the deeper, more primitive structures of the brain-stem, including possibly extra-pyramidal structures and centres in the reticular formation in the brain-stem, will be gradually carried on in our future experimental work.

V. SUMMARY.

(1) A study was made of the effects of large vestibular nuclear lesions in combination with various lesions of the 8th nerve and labyrinth in over twenty-five *Macacus rhesus* monkeys. The phenomena observed were those commonly seen in vestibular lesions of peripheral type, including nystagmus, asymmetries in posture, asymmetries in motion and inconstant changes in tone and in the reflexes.

(2) A large vestibular nuclear lesion of one side was found to produce vestibular phenomena identical in type to those of unilateral labyrinthectomy, or unilateral section of the 8th nerve, but of greater intensity and of longer duration.

(3) In light of the inequality but essential similarity of nuclear and peripheral lesions a basic experiment consisting of study of the effects of nuclear lesions following bilateral labyrinthectomy or bilateral section of the 8th nerve was made. In such cases peripheral elements were completely excluded. In these cases typical unilateral vestibular phenomena referable to the lesion of the vestibular nuclei of one side appeared. In intensity the phenomena approximated to those found in animals with large unilateral vestibular nuclear lesions alone in the presence of otherwise intact labyrinths or nerves. All of the phenomena seen in unilateral labyrinth, nerve, or large nuclear lesions in otherwise intact animals appeared in these cases.

(4) The development of typical unilateral vestibular phenomena as a result of nuclear lesions in the absence of labyrinths or nerves indicated that other afferent components enter the vestibular nuclear complex and

help in maintaining the central vestibular mechanism. The components which were first suggested included that in the juxta-restiform system connecting the vestibular nuclei with the cerebellar roof nuclei, those associated with the posterior cervical roots, and those from higher motor centres.

(5) Section of the juxta-restiform fibres connecting the cerebellar roof nuclei with the vestibular nuclear complex had been shown to produce typical vestibular signs. The signs followed section of these fibres even though both labyrinths had been previously removed. Removal of the labyrinths produced no detectable change in the symptoms associated with subsequent section of the juxta-restiform fibres.

(6) Various combinations of lesions of labyrinth, nerve and vestibular nuclei, with unilateral and bilateral lesions of 2nd, 3rd and 4th posterior cervical roots, were made.

In general it was found possible to vary by root lesions the position of the head following peripheral vestibular lesions. However, in such cases considerable variation occurred from animal to animal and the possibility is suggested that the various components play roles of varying degrees of importance in different animals. Bilateral section of the posterior cervical roots did not affect in any way the development of the typical vestibular phenomena in the region of the head produced by large unilateral vestibular nuclear lesions.

(7) Various combinations of lesions of the ear and higher motor centres were made, but the results have not been found conclusive up to date and the experiments are being continued.

(8) The most important general result of the work has been to show that typical unilateral vestibular phenomena can be produced by vestibular nuclear lesions in the monkey, even though both labyrinths and 8th nerves have been previously eliminated, thus confirming the findings of Spiegel and Sato in the dog. We feel that these experiments may serve as an experimental basis for understanding the presence of unilateral vestibular signs in patients with dead labyrinths or 8th nerves on the side to which the symptoms are referred.

REFERENCES.

[1] NORTHINGTON, P., and BARRERA, S. E. "Effects of Unilateral and Bilateral Labyrinthectomy and Intracranial Section of Eighth Nerve," *Arch. Neurol. and Psychiat*, 1934, **32**, 51-71.

[2] MAGNUS, R. "Körperstellung," 1924, pp. 404 *ff.* J. Springer, Berlin.

[3] FERRARO, ARMANDO, and BARRERA, S. E. "Effects of Lesions of the Juxta-restiform Body (I.A.K. Bundle) in *Macacus rhesus* Monkeys," *Arch. Neurol. and Psychiat.*, 1936, **35**, 13-28.

[4] SPIEGEL, E. A., and SATO, G. "Ueber den Erregungszustand der medullaren Zentren nach doppelseitiger Labyrinthausschaltung (Vestibular Ausfallerscheinungen nach einseitiger Verletzung der Vestibulariskerne trotz Labyrinthmangels)," *Pfluger's Archiv.*, 1926, **215**.

[5] HENRI, VICTOR. "Effets de la destruction du labyrinth chez le serpent," *Compt. rend. Soc. Biol.*, 1898.

[6] ARONOVITCH, B., and PIKE, F. H. "The Factors Influencing the Attitude of the Head in Animals with Injury to One Otic Labyrinth," *Science*, 1918, **47**, 519.

[7] WILSON, J. GORDON, and PIKE, F. H. "The Effects of Stimulation and Extirpation of the Labyrinth of the Ear and its Relation to the Motor System," *Phil. Trans. Roy. Soc.*, 1912, **203**, 127.

[8] NORTHINGTON, P. "Observations on some Disturbances of Vestibular Function," *N.Y. State Journ. Med.*, 1935, **35**, 56.

[9] DOHLMAN, G. "Experimentelle Untersuchungen uber die galvanische Vestibularisreaktion," *Acta otolaryng.*, 1929, Supp. **8**, 1-48.

[10] FERRARO, ARMANDO and BARRERA, S. E. "Posterior Column Fibres and their Termination in *Macacus rhesus*," *Journ. Comp. Neurol.*, 1935, **62**, 507.

[11] *Idem.* "Effects of Experimental Lesions of the Posterior Columns in *Macacus rhesus* Monkeys," *Brain*, 1934, **57**, 307.

[12] *Idem.* "The Effects of Lesions of the Dorsal Column Nuclei in *Macacus rhesus* Monkeys," *ibid.* 1936.

[13] RANSON, S. W., DAVENPORT, H. K., and DOLES, E. A. "Intramedullary Course of the Dorsal Root Fibres of the First Three Cervical Nerves," *Journ. Comp. Neurol.* 1932, **54**, 1.

[14] SHERRINGTON, C. S. "Note on the Spinal Portion of some Ascending Degenerations," *Journ. Physiol.*, 1893, **14**, 255.

[15] FERRARO, ARMANDO, and BARRERA, S. E. "The Effects of Lesions of the Dorsal Spino-cerebellar Tract and Corpus Restiforme in the *Macacus rhesus* Monkey," *Brain*, 1935, **58**, 174.

STUDIES ON THE EXISTENCE OF A PARAPHYSIS IN MAMMALIAN EMBRYOS.[1]

BY KNUD H. KRABBE (COPENHAGEN, DENMARK).

INTRODUCTION.

THE name "paraphysis" was given by Selenka in 1890 to a vesicular formation which develops from the brain-roof. Francotte, in 1887, observed the same formation and described it under the name of "anterior epiphysis." Selenka, however, must have the credit for having pointed out that the paraphysis is an independent formation, and probably a rudimentary sense-organ. Selenka was inclined to see a certain homology between the paraphysis and the acoustic organ in ascidias.

The paraphysis is situated between the dorsal sac of the diencephalon and the supraneuroporic plate of the fore-brain. Selenka supposed that the paraphysis is developed from the fore-brain, but other authors regarded it as a part of the diencephalon.

Several authors have described a paraphysis in fishes, amphibia and reptilia. I have investigated its embryological development in gongylus, lacerta, chamæleo, chelydra, chrysemys and alligator. These examinations confirmed the belief that the paraphysis develops in sauria, chelonia and ophidia as a uniform formation. It is only in crocodiles, which have no pineal organ, that the paraphysis has a different character. In the other reptiles it develops in the early stages of fœtal life, i.e. at about the same time as the epiphysis. It is seen as a small diverticle which gradually develops into a posteriorly directed oblong tube, resting posteriorly on the dorsal sac. During embryonic life the walls of the paraphysis consist of unistratified ependyma, generally cubical cells. This ependyma differs from that of the dorsal sac and the choroid plexus. I do not consider the paraphysis is related to the choroid plexus; in fact I believe that Selenka is correct in assuming a relationship between the former and the acoustic organ of tunicates.

In addition to descriptions of the paraphysis in fishes, amphibia and reptilia, there are a few accounts of this organ in bird embryos. No one, however, has systematically examined the paraphysis in mammals, and the few descriptions are mostly on human embryos. Selenka writes (without any further description): "Bis jetzt habe ich die Paraphyse bei Embryonen von Haifischen, Reptilien und Beuteltieren beobachtet." Francotte (1894) observed a well-characterized paraphysis in human embryos of about twelve weeks.

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[1] From the Tornblad Institute for Comparative Embryology, Lund, Sweden. (Director, Professor Dr. Ivar Broman).

In 1896 d'Erchia (quoted from Studnička) observed the paraphysis in the form of a single fold. Studnička does not believe the paraphysis is present in adult mammalian brains.

Werkman (1913) examined the brain of embryos of vesperugo, erinaceus and talpa. He found at the limit between diencephalon and telencephalon a diverticulum (recessus paraphyseos). From this diverticulum arose a prolongation, probably corresponding to the paraphysis in lower vertebrates.

The first detailed description of a paraphysis in the human embryo was given by Percival Bailey in 1916. In his discussion Bailey says: "Paraphysis: Just in front of the velum in each embryo is a small arch (figs. 18, 20 and 25 p.d.), relatively largest in the 19 mm. embryo, and smallest in the 32 mm. embryo. In each case it lies immediately in front of the velum transversum. In each case also, the lateral choroid plexus arises from its sides. There can be no doubt that this is the paraphyseal arch. No indication of the development of a glandular structure could be found. The resemblance of the paraphyseal arch in the 19 mm. embryo to that of the 10 mm. cat and twenty-hour chick, as described by Tilney, and of a 4 mm. embryo of platydactulus mauritanius by Tandler and Kantor, is rather striking." Hochstetter (1919) found in human embryos (17-27 mm., possibly 46 mm.) an evagination immediately in front of the limit between diencephalon and telencephalon. He regarded this evagination as a paraphyseal formation. He confirmed the findings of Werkman in vesperugo and in myotus murinus. Ivar Broman, in his book on the fœtal development of man, illustrates in fig. 327 a formation which resembles the paraphysis in a median section through the head of a human embryo (22·5 mm.).

The question about a paraphysis in man presents a certain neurosurgical interest. Sjövall (1910) and Kessel and Olivecrona (1936) suggest that possibly cysts in the foramen of Munro take their origin from a rudimentary embryonal paraphysis.

In order to try to discover an organ identical with the parapineal organ or parietal eye, I have systematically examined mammalian embryos. In certain stages of the fœtal life of some animals (talpa, lepus, spermophilus, equus, canis, lobodon and possibly vespertilio, dasypus and phocæna), I found a formation which possibly corresponds to the prepineal organ of lower vertebrates. This suggested that some mammalian embryos might possibly have a rudimentary paraphysis.

I have therefore studied the paraphyseal region in the splendid material at the Tornblad Institute for Comparative Embryology in Lund, Sweden. I wish to express my most cordial thanks to Doctor Tornblad, founder of the Institute, and to Professor Ivar Broman for permitting me to examine the preparations.

Definition of paraphysis.—In order to decide whether a formation present in a mammalian brain corresponds to the paraphysis in reptiles, it is first of all necessary to have a clear definition of the paraphysis, and in the second place to realize what errors are possible in the attempt to identify it.

In the first place it must be remembered that the paraphysis is situated in the median sagittal plane, in the transitional area between the anterior part of the dorsal sac and the postero-superior part of the supraneuroporic lamina. Further, it is tubular, saccular or disc-shaped, and it must point outwards towards the ectoderm.

One possible error is due to the fact that in many reptiles and in some mammals and birds, the dorsal sac presents an anterior and a posterior recess. The latter corresponds to what is sometimes called the suprapineal recess. In many mammalian embryos (even in reptiles) the dorsal sac, which posteriorly has a level or slightly uneven roof, is compressed from side to side at its anterior end, and, if this compressed part of the anterior recess is cut frontally it may appear in sections as a tubular formation issuing from the roof of the brain. Only examination of reconstructions of serial sections can show that this apparently tubular form is due to the section having passed through the anterior, compressed part of the dorsal sac.

The same condition is found in the supraneuroporic lamina. In some embryos it is flat, but in others there is a keel-shaped prominence in a part of its extension into the median sagittal plane. In single sections this may appear as a tubular evagination.

MATERIAL AND TECHNIQUE.

Nearly all the embryos were fixed in formalin or Bouin's fluid and stained according to Hansen's hematoxylin-eosin method. Most of the preparations were cut frontally, only a few sagittally. In order to embryos. In certain stages of the fœtal life of some animals (talpa, lepus, spermophilus, equus, canis, lobodon and possibly vespertilio, dasypus and phocæna), I found a formation which possibly corresponds to the prepineal organ of lower vertebrates. This suggested that some mammalian embryos might possibly have a rudimentary paraphysis.

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MATERIAL AND TECHNIQUE.

Nearly all the embryos were fixed in formalin or Bouin's fluid and stained according to Hansen's hematoxylin-eosin method. Most of the preparations were cut frontally, only a few sagittally. In order to determine the form of the paraphysis, wax or cardboard reconstructions were made of the paraphyseal region in several of them.

Monotremata.—It was possible to examine only one echidna embryo (or pouch-young) 20·2 mm. in length. The anterior part of the dorsal sac was prolonged forwards so as to form a round tube about 1 mm. in length and about 300μ in diameter. The recess was filled by choroid plexus. The anterior end of the recess also showed three small evaginations. Neither the recess nor these evaginations can be considered as homologous with the paraphysis, but further examinations on smaller embryos would be necessary to draw definite conclusions.

Marsupials.—The collection contained well prepared embryos or pouch-young of *Didelphys virginiana*, 5·4, 6·2, 8·8, 9 and 9·4 mm. in length.

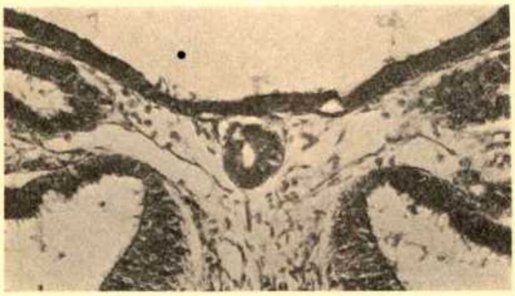

FIG. 1.—Phascolarctus. Embryo 14 mm. in length. Magnified 200. Transverse section through the paraphysis.

In the 5·4 mm. long embryo, in front of the anterior part of the dorsal sac, a formation which might possibly be identical with the paraphysis was observed. It was not, however, hollow, but a solid, pyramid-shaped protuberance from the roof of the brain, with a keel-shaped prolongation forward into the supraneuroporic plate.

None of the other oppossum embryos showed any trace of paraphysis.

The embryos of other marsupials which were examined were *Didelphys paraguayensis* (5·5 mm.), *Didelphys cancrivora* (9·5, 10 and 33 mm.), *Didelphys aurola* (13 mm.), *Phascogale* (5 mm.) and *Marmosa murina* (9 mm.). In some of the didelphydes the dorsal sac presented a small anterior recess, but in none of the above-mentioned marsupials was there any formation that could be interpreted as a paraphysis.

A 14 mm. long embryo (or pouch-young) of *Phascolarctus* showed some interesting features.

At the transition between the anterior part of the dorsal sac (which had no anterior recess) and the supraneuroporic lamina, a small, hollow, button-like diverticulum was seen in the median sagittal plane. Its cavity communicated with the ventricle. Its walls consisted of a unistratified ependyma of short cylindrical cells, the nuclei of which were round or oval and radially placed. The cells on the side of the cavity were provided with a membrane.

Its diameter was about 50 μ, its length from the posterior to the anterior end was 70 μ. It was directed posteriorly (fig. 1). A small button-shaped evagination between the posterior commissure and the habenular commissure indicated the rudiment of the pineal. The dorsal sac, between the pineal gland and the possible paraphysis, was of considerable length.

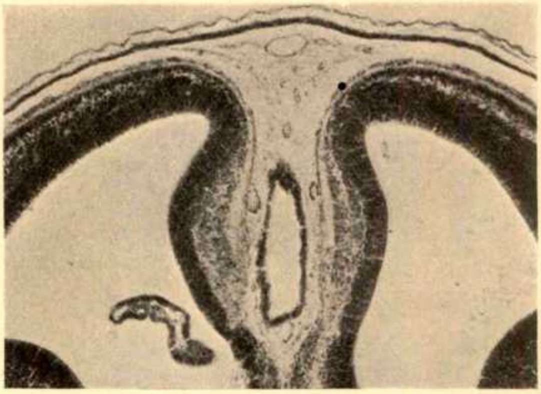

FIG. 2.—Vespertilio. Embryo 8·7 mm. in length. Magnified 75. Transverse section, "false paraphysis," anterior recess of the dorsal sac.

It is possible that this formation was one of the small evaginations which occasionally develop from the roof of the brain. In view of its position and form, however, it is not unlikely that it really is a rudimentary paraphysis.

Chiroptera.—I examined Vespertilio embryos 5, 6·5, 7·6, 8·7, 9·5 and 10 mm. in length.

In the smallest embryos the transition from the dorsal sac to the lamina supraneuroporica was smooth and without any anterior recess or paraphysis. In embryos, 7·6 and 8·7 mm. long, the posterior part of the dorsal sac was flat or slightly arched, the anterior part being compressed from side to side. The anterior end presented a sagitally compressed recessus anterior. This is a typical example of how the examination of a single section can give the false impression of the existence of a paraphyseal formation (fig. 2).

Rodentia.—The following rodent embryos were examined, *Cavia cobaya* (9·5, 11·6 and 16 mm.), *Lepus cuniculus* (4, 5, 7, 8 and 9·5 mm.), *Mus musculus* (6, 6·5, 7, 7·5, 8 and 10 mm.) and *Sciurus* (7·3, 9 and 42 mm.).

In the Cavias the dorsal sac presented a small anterior recess, but none of these embryos had a paraphysis.

The collection of the Tornblad Institute contained an extraordinarily fine group of embryos of *Spermophilus*. I examined embryos 3·5, 4·5, 6, 7, 7·5, 8, 9·5, 10, 14·5, 16·5, and 18·5 mm. in length. I have already published an account of the development of the pineal body in these embryos. The first trace of it is found in the 7 mm. embryo as a tubular formation arising from the diencephalic roof and directed towards the ectoderm. As in the Chiroptera, the posterior part of the dorsal sac is slightly arched, the anterior part being scaphoidly compressed. In some of the embryos (7, 7·5, 8 and 10 mm.) this anterior part of the dorsal sac presented small button-like excrescences. No paraphyseal formation was found between the dorsal sac and the supraneuroporic lamina.

Procavia.—A 15 mm. long embryo showed a small anterior recess from the dorsal sac, but no paraphysis. In a 16 mm. long embryo there was neither a paraphysis nor an anterior recess.

Ungulates.—In embryos of *Sus scropha*, 7·2, 10·5, 14, 16 and 22 mm. long, no paraphysis was seen.

In two embryos of *Equus caballus*, 18·5 and 23 mm. in length, a sufficiently accurate examination was not possible.

In embryos of *Capreolus caprea* (5 and 18·6 mm.) of *Ovis aries* (25·5 mm.) and in *Bos taurus* (5·6, 7, 15·5, 19 and 22 mm.) no paraphysis was observed.

Cervus dama (26 mm.) presented a rather large anterior recess but no paraphysis.

Edentates.—In embryos of *Bradypus* (20 mm.), *Dasypus* (33 mm.), and *Tamandua tetradactyla* (12·2 mm.) no trace of a paraphysis could be discovered.

In *Tatusia peba* the dorsal sac was prolonged in a narrow slit-like, sagittally situated anterior recess, but there was no paraphysis.

Pinnipedia.—Embryos of *Lobodon* (13, 29 and 62·5 mm.), *Leptonychotes weddelii* (23 mm.) and *Phoca vitulina* (48 mm.) had very large anterior recesses from the dorsal sac, but no paraphysis was observed in any of them.

Carnivora.—*Felis domestica.* In a 5 mm. embryo no trace of epiphysis or paraphysis was observed. In a 9 mm. embryo the anterior part of the dorsal sac was compressed from side to side. It was pseudotubular in isolated sections, but no paraphysis was seen.

The 12 mm. embryo presented a more peculiar appearance. The anterior recess of the dorsal sac had on either side a low evagination, and between these a short tubular or saccular projection was seen (fig. 3). It is possible that this formation was identical with the paraphysis, but it could not be proved. A 14 mm. embryo presented a similar diverticulum, but it was more tubular or saccular in form.

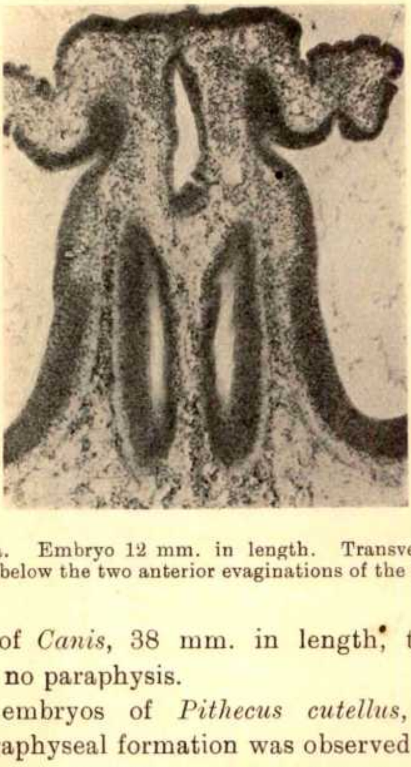

FIG. 3.—Felis domestica. Embryo 12 mm. in length. Transverse section, paraphyseal formation (below the two anterior evaginations of the dorsal sac).

In an embryo of *Canis*, 38 mm. in length, there was a small anterior recess but no paraphysis.

Primates.—In embryos of *Pithecus cutellus*, 2 and 8.7 mm. respectively, no paraphyseal formation was observed.

An embryo, 18 mm. in length, of *Brachyurus melancephalus* had a small formation in the "paraphyseal place" which deserved consideration. It was a hollow, cellular formation with folded walls of the same structure as the roof of the diencephalon. It was situated outside the roof of the brain and separated from it by a thin layer of mesenchyma. It had no communication with the roof. It is possible it is analogous with the paraphyseal formation observed in some other mammals.

In a *Hapale* embryo, 25 mm. in length, there were small excrescences from the roof of the brain, but as the preparation was badly preserved no definite conclusions could be drawn. Further examinations of well-prepared material are needed.

Homo.—The smallest embryos examined, 4·1, 11, 14, and 17 mm., showed no sign of paraphysis, but embryos 21, 22·5 and 25·5 mm. in length presented a formation which seemed to correspond to the paraphysis of lower vertebrates.

In the 21 mm. embryo cut frontally (fig. 4), just in front of the anterior end of the dorsal sac, a small button-shaped evagination, growing outward from the upper part of the supraneuroporic lamina, was seen. The walls of these evaginations were somewhat thicker than those of the adjacent parts of the brain-roof. They consisted of cells with oblong nuclei, arranged radially in four or five rows. The form of the nuclei varied: some were short, other more rod-shaped. On the whole, the nuclei did not contain much chromatin. The structure of the wall of this paraphyseal formation differed from the ependyma of the dorsal sac, as well as from the ependyma of the choroid plexus.

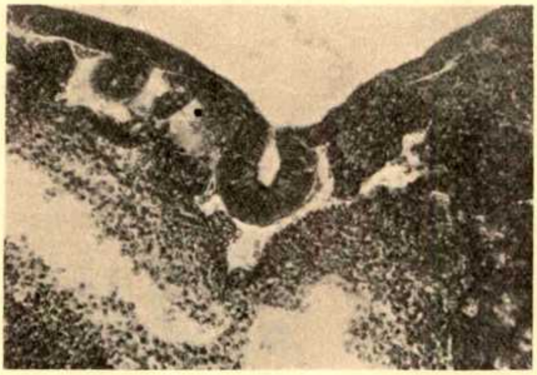

FIG. 4.—Homo. Embryo 21 mm. Magnified 200. Frontal section, paraphyseal formation.

An embryo, 22·5 mm. in length,[1] cut in the sagittal plane, presented a similar picture (fig. 5). The oblong nuclei, which contained little chromatin, were arranged in three or four rows. The protoplasm was most abundant in those parts of the cells adjoining the cavity. It may be mentioned that in this stage of development the pineal body had a double "anlage" consisting of a massive anterior part on the front wall of the evagination.

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[1] The embryo is the same as that described in Broman's book.

An embryo, 25·5 mm. in length, had an evagination of paraphyseal nature (fig. 6). The anterior part of the dorsal sac presented a bilateral anterior recess directed forwards, similar to that seen in the cat. A little in front of and between these two evaginations, the roof of the brain was elevated so as to form a hollow tap-shaped prominence which was directed forwards; its cavity did not appear to communicate with the ventricle of the brain. The walls consisted of an ependyma with three or four rows of oblong, radially placed nuclei, which were poor in chromatin. The protoplasm was arranged as in the two former

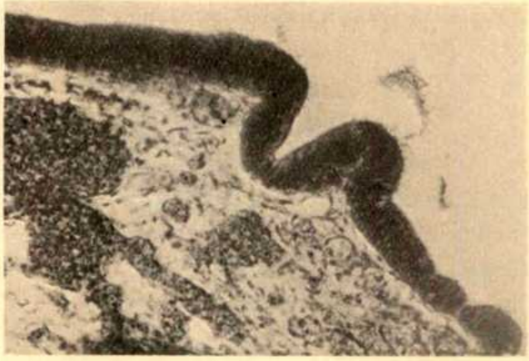

FIG. 5.—Homo. Embryo 22·5 mm. Magnified 75. Sagittal section, paraphyseal formation.

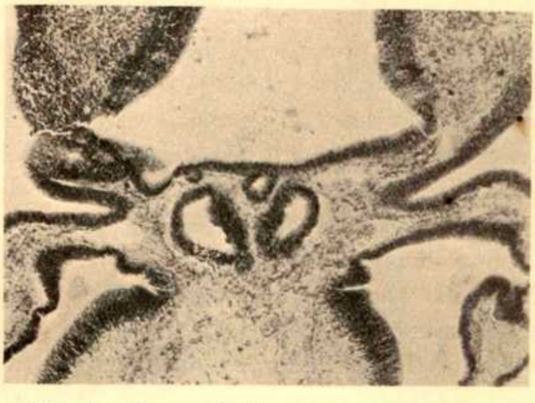

FIG. 6.—Homo. Embryo 25·5 mm. in length.

embryos. Even in this embryo the ependyma differed from that of the dorsal sac and the choroid plexus.

In the older embryos (29, 35, 35·5, and 50 mm. respectively) the dorsal sac had an anterior recess from the wall of which several more or less irregular prominences projected. In front of the dorsal sac, however, there was no evagination corresponding to a rudimentary paraphysis.

SUMMARY.

Examination of an extensive collection of mammalian embryos was undertaken for the purpose of determining the existence of a (rudimentary) paraphysis. The following results were obtained:—

In the majority of the embryos examined there was not found at any stage a formation which might be regarded as a rudimentary paraphysis. This is particularly true with regard to a complete series of Spermophilus and Vespertilio embryos. In many embryos the anterior wall of the dorsal sac, i.e., the recessus anterior, forms a cupular prominence which might be mistaken for a paraphysis. In three mammals there were structures which required a more detailed study.

In a 14 mm. long embryo of Phascolarctus there was found at the transition between the anterior part of the dorsal sac and the lamina supraneuroporica, which corresponds to the site of the paraphysis in reptiles, a tubular formation issuing from the roof of the brain which was directed backwards. It is impossible to prove with certainty that this corresponds to the paraphysis in reptiles. In many vertebrate embryos there are evaginations from the roof of the brain, but when the diencephalon of Phascolarctus is compared with that of reptiles, and when we take into account the position and development of this structure, it presents a striking resemblance to the paraphysis in reptiles.

In 12 and 14 mm. long cat embryos, as in several other embryos, both sides of dorsal sac had evaginations which pointed forward. Between these there was a saccular thin-walled evagination from the roof of the brain which was possibly a rudimentary paraphysis.

Finally, the paraphyseal region in man presents striking features previously observed by Percival Bailey and Ivar Broman. In several embryos of about 20 mm. (seventy-five days) an outwardly directed evagination was visible at the place of transition between the dorsal sac and the supraneuroporic lamina. The form and position of this evagination indicates that it is a rudimentary paraphysis. It is, however, only a transitory structure, but it is striking that at a certain stage of development even man seems to have this phylogenetically old formation which has probably disappeared in most other mammals.

BIBLIOGRAPHY.

Bailey, Percival. "Morphology of the Roof Plate of the Forebrain and the Lateral Choroid Plexus in the Human Embryo," *Journ. Compar. Neurology*, 1916, **26**, 79.

Broman, Ivar. "Manniskans utveckling forre fodelsen," p. 808. Lund, 1927.

d'Erchia, F. "Contributo all' studio della volta del cervello intermedio e della regione parafisaria in embrioni di pesci e mammiferi," *Monitore zool. ital.*, 1896, **7**.

Francotte, P. "Contribution à l'étude du développement de l'épiphyse et du troisième oeil des reptiles," *Bull. de l'acad. roy de Belg.*, 1887.

Idem. "Note sur l'oeil pariétal, l'épiphyse, la paraphyse et les plexus choroides du troisième ventricule," *Ibid.*, 1894, 3ème, série 27.

Hochstetter, F. "Beiträge zur Entwicklungsgeschichte des menschlichen Gehirns." I. Wien, 1919.

Kessel, F. K. and Olivecrona, H. "Über Foramen-Monroi-Cysten. Zentrabl. f. Neurochirurgie." 1936, **1**, 18.

Krabbe, Knud H. "Recherches sur l'existence d'un oeil pariétal rudimentaire (le corpuscle pariétal) chez les mammifères. Biological Reports of the Royal Danish Academy of Sciences." Copenhagen, 1929, **8**, 3.

Idem. "Recherches embryologiques sur les organes pariétaux chez certaines reptiles Biological Reports of the Royal Danish Academy of Sciences." Copenhagen, 1935, **12**, 3.

Selenka, E. "Das Stirnorgan der Wirbeltiere," *Biol. Centralbl.*, 1890-1891, **10**, 323.

Sjovall, E. cit Kessel-Olivecrona.

Studnička, F. K. "Die Parietalorgane." Oppel's "Lehrbuch der vergleichenden Anatomie der Wirbeltiere," Jena, 1905, **5**.

Werkman, H. "L'évolution antagénique de la paroi antérieure du cerveau. Arch. néerland, des sciences exactes et naturelles." S. III B. Vol. 2, 1917 (1913).

PERIODIC SOMNOLENCE AND MORBID HUNGER: A NEW SYNDROME.

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DEFINITION OF THE SYNDROME.

THE purpose of this paper is to call attention to a syndrome characterized by recurring periods of somnolence and morbid hunger, and to suggest a possible explanation of the cause of this syndrome based on clinical and experimental data on the relation of the frontal lobes to gastro-intestinal motility.

By *periodic somnolence* I mean somnolence lasting days or weeks. There are other cases of somnolence in which the attacks last several minutes; these cases should not be confused with those I am about to discuss.

In the cases with which we are here concerned, then, there are attacks of sleepiness lasting from several days to several weeks. The longest recorded was three months. During the attack the patient sleeps excessively day and night, in extreme instances waking only to eat and go to the toilet. He can always be roused. When roused he usually is irritable and wants to be let alone so that he can go back to sleep. He is abnormally hungry and eats excessively. These attacks are separated by intervals of normal health. Besides the two main symptoms, somnolence and hunger, there are certain incidental symptoms to be mentioned later.

Ten cases of this syndrome have been reported. They may be divided into seven "good" and three "doubtful" cases.

"Good" cases.—Kleine (1925) reported five cases of periodic somnolence. In Cases 3 and 4 there was increased appetite during the attacks.

Kleine's Case 3. Male, 17. The first attack occurred at 13½ years. Six attacks had occurred by the time the article was written. The first lasted three weeks, the second several days, and the remaining four about ten days each. During the attacks the patient slept almost all the time, and, when awake, complained of headache and fatigue and was abnormally hungry.

Kleine's Case 4. Male, 19. The first attack of sleepiness occurred at 15. The number of attacks is not given. In three of them he was under medical observation. These three lasted five days, two weeks and two weeks. The patient was sleepy, restless and complained of fatigue and dizziness. Hunger is specifically mentioned in the description of the last attack; it was noted that he had increased appetite and stole the food of a fellow-patient.

Lewis' Case 4 (1926). Male, 12. The patient had five attacks, the first at 10. They lasted from two weeks to three months. They "were in the main similar and characterized by weakness, dazed facial expression, gluttony and sleepiness."

Levin's Case 7 (1929). This was a boy studied at the Henry Phipps Psychiatric Clinic. I shall not repeat the details already published, but shall summarize certain features of the case and shall report the outcome.

The first attack occurred at 16. There were nine in all. The following table shows the date and duration of each, and the length of the intervals.

Number of attack	Date	Duration	Length of the subsequent interval
1	May, 1925	2 weeks	2 weeks
2	June, 1925	1 week	3½ ,,
3	July, 1925	1 ,,	5 months
4	December, 1925	4 weeks	5 ,,
5	July, 1926	6 ,,	5 ,,
6	January, 1927	3 ,,	5 ,,
7	July, 1927	6 ,,	8 ,,
8	April, 1928	6 ,,	7 ,,
9	December, 1928	6 ,,	

In a series of letters, the last of which was written on June 24, 1935, the patient's mother reported that there were no further attacks. The ninth and last attack was the mildest of all.

In his attacks the patient was dull and sleepy. In the first few days of the attack he slept constantly, and woke only to eat and go to the toilet. In the remainder of the attack he slept much by day, though not constantly, besides sleeping through the night. His appetite was enormous: he ate large meals and much between meals.

Ever since the last attack he has been in perfect health. It is perhaps significant that in the six months after the last attack he was under active dental treatment and had six teeth extracted. I have had no report from his dentist. In a letter on February 14, 1934, his mother said he weighed 150 lb. (as compared with 121 and 131 on his two admissions to the Phipps Clinic in 1926). In her last letter, June 24, 1935, she said he " is just fine, never sick, has had no attacks of sleepiness, weighs 150 lb., works steadily. . . . He is 26 years old and has been married two weeks."

Daniels (1934), after referring to my case, gave a brief account of a similar case of his own. " A youth, aged 18, had had four similar attacks of about the same length during the two years preceding his admission to the clinic. . . . (He) was docile otherwise, but was difficult to manage during the attacks, and, like Levin's patient, had a ravenous appetite. When seen in the clinic toward the end of a period of somnolence, he appeared dull and apathetic, but was nevertheless restless and would not co-operate very well."

Kaplinsky and Schulmann (1935) have published two articles bearing on this discussion. Case 2 in their first article, and Case 1 in their second, may be regarded as " good " cases.

Case 2, in their first article, is that of a young man who began to have periods of somnolence at 14. The report covers five years, during each of which he had the following number of attacks: 7, 3, 2, 2 and 1. They usually lasted from one to three weeks; one of the early ones lasted six weeks. The authors make three references to his extraordinary appetite. Thus, during an attack which they observed, " he eats much, asks for apples, and devours them in large quantities."

Case 1, in their second article, is that of a young man who had his first period of somnolence at 17. At the time the article was written he had had five attacks, in November, 1930, December, 1930, March, 1932, April, 1932, and January, 1933. They lasted from five to seven days. Increased appetite is mentioned in the account of the first attack only: " He ate more than usual. . . . Everything one brought him he bolted avidly and even seized the food of other patients " (page 348).

" Doubtful " cases.—Kaplinsky and Schulmann's first article deals with four cases. Two of these are their own. The other two were reported in Russian journals by Anfimoff (1898) and Kanabich (1923) respectively. I have already cited their Case 2 as a " good " case. The remaining three, because of meagreness of details concerning appetite, are put down here as doubtful. Speaking of their Case 1, Kaplinsky and Schulmann say only that in her first attack of somnolence the patient " rather often asked for and drank milk." In their account of two later attacks, in which they studied her, they make no mention of morbid hunger. Indeed, concerning one of these attacks, they say: " One must repeatedly awaken her and coax her to eat." In their extended summary of Kanabich's case there is no mention of appetite.

In their briefer summary of Anfimoff's case, the only statement about appetite is that the patient recalled that in his first attack his appetite was "ausgezeichnet," which means excellent without necessarily implying excessive. Nevertheless it should be noted that in their discussion of these four cases taken as a group, Kaplinsky and Schulmann say that in all four there was increased appetite.

PATHOGENESIS OF THE SYNDROME.

The best clue to the pathogenesis of "periodic somnolence-hunger"—a crude but convenient designation for the syndrome under discussion—lies in recent experimental work on lower animals by Fulton and others which, taken together with clinical evidence in human beings, demonstrates the existence in the frontal lobes of centres which regulate gastro-intestinal motility.

Fulton and his co-workers [7] found that after bilateral removal of parts of the frontal lobes in monkeys and chimpanzees there is "increase in appetite, which sometimes involves the ingestion of two or three times the normal amount of food, and despite this circumstance the animals generally lose weight." No elevation of the basal metabolic rate was found which might explain this increase in appetite [8]. Moreover, in animals thus treated intussusception appeared with significant frequency as a cause of death [8]. Finally, Mettler and his co-workers, working with cats, found that removal of frontal cortical tissue leads to gastro-intestinal hypermotility demonstrable fluoroscopically after a barium meal. Thus it is evident that the frontal lobes of lower animals contain centres which inhibit gastro-intestinal motility, and loss of which produces excessive motility of the gut and, as a consequence, increased hunger.

A circumstance which on first thought might seem to be at variance with the foregoing conclusion is the fact that hyperperistalsis and intussusception may also be produced by stimulating certain frontal areas [8, 24]. But, as Fulton has pointed out [8], "this somewhat surprising paradox is in harmony with the belief that the cortex contains both excitatory and inhibitory elements, and that the result of stimulation from any given point is necessarily an algebraical summation of effect." The foregoing conclusion may therefore be permitted to stand.

These experimental data lend great significance to a series of human cases in which morbid hunger was observed in association with injury, abscess and tumour of the brain, especially of the frontal lobes. These cases will be mentioned briefly.

Stephen Paget (1897) described fourteen cases of "voracious hunger and thirst from injury or disease of the brain," thirteen of them being cases culled from the literature and one a case reported by himself in 1891. In eleven there was severe head injury; in one, suppuration of the ear and petrous bone; in one, cerebral abscess following otitis media, and in the last, cerebral embolism.

Four more traumatic cases were subsequently reported; one by Sollier and Delagenière; one by Perimov (cited by Bechterew [3], vol. iii, page 1645); and two by Brouwer (cited by Frazier).

There are five cases of tumour. Mills' Case 1 is that of a boy who had a ravenous appetite in the last week of his life. Autopsy showed a tumour of the frontal lobe. In Spiller's Case 3 there was a tumour of the pons. Frazier's paper, dealing with tumours of the frontal lobes, is of special interest. In his series of 105 cases, three showed morbid hunger: Cases 5 and 8, in which the tumour was limited to the frontal lobe, and Case 9, in which the temporal lobe also was involved.

In considering the pathogenesis of the syndrome we must account for the presence of two symptoms, morbid somnolence and morbid hunger. In view of the experimental and clinical evidence already cited, there is a possibility that the morbid hunger may be caused by paralysis of those frontal centres which inhibit gastro-intestinal motility. Morbid somnolence is a disputed problem. Many writers assume it necessarily points to a lesion of the "sleep centre" in the neighbourhood of the 3rd ventricle. This seems too narrow a view. The characteristics of sleep suggest not only a disturbance of certain lower centres, but of the highest centres as well. When one is asleep his comprehension of events in the external world is dulled if not abolished; his thinking is reduced to a primitive level (dreams); and voluntary movement is at a standstill. These are "symptoms" of loss of function of the highest cerebral centres. Therefore, in considering the nature of sleep it is illogical to confine attention to a subcortical sleep centre; the highest centres too deserve attention, since they obviously are in abeyance. This statement, which is, I think, self-evident, is powerfully supported by Pavlov's demonstration that in sleep there is widespread cortical inhibition.

I do not deny that in some cases a lesion of the sleep centre is the probable cause of morbid somnolence, but it is equally probable that in other cases morbid somnolence may be caused by abnormal exhaustibility or "inhibitability" of the highest cerebral centres. This matter was discussed more fully in a paper on the role of the cerebral cortex in narcolepsy [15] and need not be gone into further here. Of all the possible explanations that suggest themselves for the syndrome of periodic somnolence-hunger, the simplest (since it would account for both symptoms, somnolence and hunger, by a single lesion) is to assume a state of undue inhibitability of the highest cerebral centres, including those frontal centres, which inhibit gastro-intestinal motility. These centres are so constituted, or so altered by disease, as to be unduly inhibitable or exhaustible, and now and then they become exhausted —a circumstance which gives rise to morbid sleep and hunger, which persist until they have recovered from their exhaustion.

INCIDENTAL FEATURES OF THE SYNDROME.

Certain incidental features may now be mentioned. Though incidental, they are important for an understanding of the mechanism of the syndrome.

Motor unrest.—Conspicuous motor unrest during attacks of somnolence-hunger occurred in five of the seven "good" cases (Kleine's Cases 3 and 4; Lewis; Levin; and Daniels). This unrest, as well as other symptoms to be mentioned presently, are shown not so much when the patient is asleep as when he temporarily wakes up.

On the hypothesis offered above regarding the pathogenesis of periodic somnolence-hunger, the occurrence of motor unrest in this syndrome is easily explained. One of the principles of the physiology of the highest cerebral centres is that they inhibit the activity of lower centres, and that paralysis of the highest "releases" the lower. Paralysis of the highest motor centres may thus produce motor hyperactivity. Hughlings Jackson offered this principle in explanation of motor hyperactivity occurring in a variety of disorders. Thus, the excitement of an epileptic after a fit and that of a man intoxicated with alcohol are alike due to the release of lower centres from the control of higher centres that have been paralysed, in the one case from post-epileptic exhaustion, in the other from the poisonous action of alcohol. Directly bearing on the problem under discussion is the fact that Fulton [7], in the experiments with monkeys cited above, found that bilateral removal of certain frontal areas produces (besides the excessive appetite already mentioned) marked restlessness.

Mental symptoms.—These include excitement, irritability, difficulty in thinking, forgetfulness, incoherent speech and hallucinations. They occurred to a varying extent in all the seven "good" cases (*see* accompanying table) and were conspicuous in some. It should be emphasized that mental symptoms and motor unrest occurred only during the attacks of somnolence-hunger; in the intervals there were no symptoms whatever.

TABLE.

	"GOOD" CASES							"DOUBTFUL" CASES		
	Kleine's Case 3	Kleine's Case 4	Lewis	Levin	Daniels	Kaplinsky and Schulmann's first paper, Case 2	K. and S. second paper, Case 1	Aufimoff	Kanabich	K and S. first paper, Case 1
Sex	M.	M.	M.	M.	M.	M.	M.	M.	M.	F.
Age of onset	18	15	10	16	16	14	17	19	18	12
Incidental symptoms in the attacks—										
Motor unrest	×	×	×	×	×					
Excitement						×	×			
Irritability	×	×	×	×	×		×		×	
Difficulty in thinking	×		×	×			×			
Forgetfulness			×	×		×				
Incoherent speech	×									
Hallucinations	×	×	×			×				

It would be beyond the scope of this paper to consider in detail the pathogenesis of these mental symptoms. It will suffice to make the general statement that certain mental symptoms presuppose some degree of paralysis of the highest cerebral centres. This follows from the view which Jackson never tired of asserting, viz. that mind is an immaterial thing whose manifestations are concomitant with processes in a material substrate (the highest cerebral centres, the "organ of mind"). I have already discussed this matter at some length in two papers on the psychiatric application of Jackson's theories [14, 16]. Here I shall merely suggest that in periodic somnolence-hunger the inhibition of the highest cerebral centres that can explain an attack of somnolence can also explain the mental symptoms that occur in the attack.

Insomnia at the close of an attack.—In five of the "good" cases (Kleine's Cases 3 and 4; Levin; Case 2 in Kaplinsky and Schulmann's first paper, and Case 1 in their second) and one of the "doubtful" (Case 1 in Kaplinsky and Schulmann's first paper) it was noted that sometimes at the close of an attack of somnolence-hunger there was insomnia for the greater part of one night. Two of these cases will be cited in illustration. My patient's fourth attack began to clear up on January 1, 1926, when he said, "I'm beginning to come out of it." He continued sleepy and irritable. On January 3, for the first time in this attack, he found it hard to fall asleep at night, and lay awake reading until 2 a.m. on January 4, after which he slept six hours. When he awoke, it was evident from his bright, alert and agreeable manner that the attack had reached its close. He said "I feel like I woke up again." Subsequent observation showed that the attack was over. In Case 1 in Kaplinsky and Schulmann's second paper, the attack of November, 1930, began to ease up on the afternoon of the seventh day. The patient felt better but had no desire to get up until evening, when he felt perfectly restored. He spent the evening conversing with fellow-patients, and could not fall asleep until daylight. The same thing happened in the attack of January, 1933.

A similar observation was made in methyl chloride intoxication by Baker. Industrial workers exposed to methyl chloride for a long time develop neurological symptoms, including pronounced somnolence, which clear up when the exposure is stopped. Baker noted that "as the symptoms of intoxication diminished, a persistent insomnia occurred in fifteen (out of twenty-one) cases, which necessitated the use of hypnotics." (Incidentally there is no mention of morbid hunger in these cases.)

Evidently a long continued inhibitory state may be followed by a state in which inhibition is temporarily impossible. Inhibition is self-correcting, in the sense that while in the inhibitory state nerve cells undergo reparative changes which eventually cause the lifting of the inhibition and, for a certain length of time, prevent its return. But the manner in which this occurs is not known. Nothing is known of the physical and chemical changes that occur in nerve cells when they pass into, or out of, the inhibitory state.

Sex; *Age of onset.*—Data on these points are striking. All the seven "good" cases and two of the three "doubtful" were in males (the exception being Case 1 in Kaplinsky and Schulmann's first paper). The age of onset was, without exception, in the second decade (*see* table).

Onset soon after an acute illness.—In four cases (three of the "good" and one of the "doubtful") the first attack of somnolence-hunger occurred soon after an acute illness. The facts are these: (1) In Kleine's Case 3 the patient was laid up in August, 1918, with an illness resembling "grippe" which lasted ten or twelve days. When he got up at the end of this illness he became confused and talked and acted foolishly. This lasted eight to ten days and was followed by complete recovery. A month later there occurred another attack, designated by Kleine as a sleep attack. In the third attack, a month later, morbid hunger was noted for the first time. It is noteworthy that the patient then remained well for almost three years, until August, 1921, when he had his fourth attack. (2) In the case which I have reported (1929) the patient, on April 24, 1925, took part in an athletic meeting in the rain. April 27 he complained of sore throat and felt feverish. A physician diagnosed tonsillitis. April 29 he complained of severe occipital pain and tossed in bed until midnight. April 30 he fell asleep without difficulty. May 1 he felt well enough to attend a banquet in the evening. On his return home he was taciturn, which was unusual for him. May 2 he continued taciturn. May 3, at 4 p.m., he fell asleep and slept all afternoon, evening and night. This was the beginning of his first attack of somnolence-hunger. (3) In Daniels' case the first attack occurred soon after recovery from influenza. (4) In one of the "doubtful" cases, reported by Kanabich and cited by Kaplinsky and Schulmann in their first paper, the first attack came during convalescence from measles.

In Kleine's Case 4 one of the attacks (not the first) occurred soon after antityphoid inoculation.

Improvement and cure.—In most of the cases there was little or no improvement at the time they were reported. By contrast, in two cases there was marked improvement as indicated by diminution in the frequency of attacks, while in a third and possibly a fourth they ceased entirely.

Cessation of the attacks occurred in my case. The patient's last attack was in December, 1928, and subsequent reports, the last of which was in June, 1935, showed that he had continued uninterruptedly well. During the six months that followed the last attack he received active dental treatment and had six teeth extracted. It is therefore possible that focal infection played a role in causing the lesion of his highest cerebral centres. But a glance at the table on page 495 will show that from the beginning there was progressive lengthening of the intervals between attacks, so that it is also possible that the cure was spontaneous.

In Kleine's Case 3 the patient had no attacks in the one and a half years that followed the last. The subsequent course is not known.

Striking diminution in frequency, but not cessation, of attacks occurred in the two cases reported by Kaplinsky and Schulmann in their first paper—Case 1 (a "doubtful" case) and Case 2 (a "good" case). In Case 1 the number of attacks in successive years of the disease was 20, 18, 14, 14, 4, 3, 2, 1, 1; in Case 2: 7, 3, 2, 2, 1.

MORBID HUNGER IN RELATION TO BRIEF PAROXYSMS OF SLEEP.

Reference may be made to two cases in which there was hunger in relation to paroxysmal somnolence—cases in which the attacks last only a few minutes. Daniels mentioned a narcoleptic child who "complained of hunger immediately before his attacks of sleep." Devic's Case 4, on the other hand, is that of a narcoleptic who often complained of hunger on waking from a sleep attack. These cases may be understood if one remembers that the component parts of the highest centres do not always proceed simultaneously in their passage into, or recovery from, inhibition.

SUMMARY.

From the literature are cited seven cases of what may be called "periodic somnolence-hunger," a syndrome characterized by attacks, usually lasting several days or weeks, in which the patient is excessively sleepy and hungry. Besides these cardinal symptoms, the attacks may be further marked by motor unrest and by mental symptoms (irritability, difficulty in thinking, forgetfulness, incoherent speech and hallucinations). All these symptoms vanish in the intervals between attacks. The seven cases were all in males, and in each the onset was in the second decade. In three the onset occurred soon after an acute illness (respectively, "grippe," sore throat with fever, and "influenza").

Fulton and others have shown that the frontal lobes contain centres which inhibit gastro-intestinal motility, their excision causing increased appetite, gastro-intestinal hypermotility and intussusception. These centres form part of the highest cerebral centres, more specifically, of the highest motor centres. The hypothesis is offered that "periodic somnolence-hunger" is due to excessive "inhibitability" or exhaustibility of the highest centres. The untimely and prolonged inhibition of these centres will explain the manifestations of the syndrome. Inhibition of the highest cerebral centres will explain the somnolence and the mental symptoms; inhibition of the centres described by Fulton, the hunger and the motor unrest.

Excessive inhibitability of the highest centres is probably the result of some alteration of their component cells.

BIBLIOGRAPHY.

[1] Anfimoff, J. A. Cited by Kaplinsky and Schulmann [10].

[2] Baker, H. M. "Intoxication with Commercial Methyl Chloride," *Journ. Amer. Med. Assoc.*, 1927, **88**, 1137-1138.

[3] Bechterew, W. von. "Die Funktionen der Nervencentra." Jena: 1911.

[4] Daniels, L. E. "Narcolepsy," *Medicine*, 1934, **13**, 1-122.

[5] Devic, A., Morin, G., and Poisson, G. "La cataplexie," *Journ. de méd. de Lyon*, 1932, **13**, 397-403.

[6] Frazier, C. H. "Tumor Involving the Frontal Lobe Alone," *Arch. Neurol. and Psychiat.*, 1936, **35**, 525-571.

[7] Fulton, J. F., Jacobsen, C. F., and Kennard, M. A. "A Note Concerning the Relation of the Frontal Lobes to Posture and Forced Grasping in Monkeys," *Brain*, 1932, **55**, 524.

[8] Fulton, J. F. "Some Functions of the Cerebral Cortex," First Lecture, *Journ. Michigan State Med. Soc.*, 1934, **33**, 175-182.

[9] Kanabich, J. W. Cited by Kaplinsky and Schulmann [10].

[10] Kaplinsky, M. S., and Schulmann, E. D. "Ueber die periodische Schlafsucht," *Acta Medica Scandinavica*, 1935, **85**, 107-128 and 346-376.

[11] Kleine, W. "Periodische Schlafsucht," *Monats. f. Psychiat. u. Neurol.*, 1925, **57**, 285-320.

[12] Levin, M. "Narcolepsy (Gélineau's Syndrome) and Other Varieties of Morbid Somnolence," *Arch. Neurol. and Psychiat.*, 1929, **22**, 1172-1200.

[13] *Idem.* "The Pathogenesis of Narcolepsy, with a Consideration of Sleep-paralysis and Localized Sleep," *Journ. Neurol. and Psychopath.*, 1933, **14**, 1-14.

[14] *Idem.* "Hughlings Jackson's Views on Mentation; their Value for the Psychiatrist," *Arch. Neurol. and Psychiat.*, 1933, **30**, 848-874.

[15] *Idem.* "The Role of the Cerebral Cortex in Narcolepsy; the Classification of Narcolepsy and Allied Disorders," *Journ. Neurol. and Psychopath.*, 1935, **16**, 236-241.

[16] *Idem.* "On the Causation of Mental Symptoms: an Inquiry into the Psychiatric Application of Hughlings Jackson's Views on the Causation of Nervous Symptoms, with Particular Reference to their Application to Delirium and Schizophrenia," *Journ. Mental Science*, 1936, **82**, 1-27.

[17] Lewis, N. D. C. "The Psychoanalytic Approach to the Problems of Children under Twelve Years of Age," *Psychoanalytic Review*, 1926, **13**, 424-443.

[18] Mettler, F. A., Spindler, J., Mettler, C. C., and Combs, J. D. "Disturbances in Gastro-intestinal Function after Localized Ablations of Cerebral Cortex," *Arch. Surg.*, 1936, **32**, 618-623.

[19] Mills, C. K. "Two Cases of Brain Tumor," *Journ. Nerv. and Ment. Dis.*, 1887, **14**, 707-715.

[20] Paget, S. "A Case of Cerebral Abscess, Twice Trephined: Hernia Cerebri: Recovery," *Trans. Clin. Soc. London*, 1891, **24**, 192-197.

[21] *Idem.* "On Cases of Voracious Hunger and Thirst from Injury or Disease of the Brain," *ibid.*, 1897, **30**, 113.

[22] Sollier, P., and Delagenière, H. "Le centre cortical des fonctions de l'estomac d'après un cas d'abcès du cerveau d'origine traumatique," *Rev. Neurol.*, 1901, **9**, 1103.

[23] Spiller, W. G. "Brain Tumor," *Journ. Amer. Med. Assoc.*, 1909, **53**, 2078.

[24] Watts, J. W., and Fulton, J. F. "Intussusception—the Relation of the Cerebral Cortex to Intestinal Motility in the Monkey," *New Eng. Journ. Med.*, 1934, **210**, 883-896.

NOTICES OF RECENT PUBLICATIONS.

The Comparative Anatomy of the Nervous System of Vertebrates, including Man. By C. U. ARIËNS KAPPERS, G. C. HUBER and E. C. CROSBY. New York: The Macmillan Company. 1936. Two Volumes. Pp. 1,845. Price £3 3s.

The appearance sixteen years ago of Kappers' "Vergleichende Anatomie des Nervensystems" was an important event in the study of the structure of the brain, for by bringing together in it all that was then known of the anatomy of the nervous system, and by adding to it from his own unrivalled experience of its comparative morphology, he provided a textbook in which the phylogenetic history and the development of each portion of the nervous system was clearly presented. The volume under review originated from an endeavour to provide an English translation of Kappers' textbook, but while this progressed so many additions became necessary as further knowledge accumulated that it was decided to rewrite almost all the chapters. The original plan has been, however, followed, but most of the sections have been extended and a large number of new illustrations are included. The bibliography has been brought up to date and the method of reference in the text has made it easier to identify authorities quoted.

The first volume opens with a chapter on the evolution and morphology of the nervous elements, and a consideration of the laws that determine the building up of the nervous system. It deals also with the spinal cord, medulla and cerebellum. The anatomy of the important structures contained in the mesencephalon and diencephalon is described in great detail and richly illustrated in the first part of the second volume, the rest of which is devoted to the forebrain of all vertebrate classes and particularly of man. From these chapters the reader can obtain, as nowhere else, a clear picture of the evolution of the structure of the central ganglia as well as of the cortex, and though deductions from structure to function are always risky, an acquaintance with the phylogenetic history of an organ cannot but broaden the student's conception of its mode of working. In this lies the practical utility of such a comparative anatomy, but as here presented it is also a fascinating study. The volumes are excellently written and arranged, and the text and illustrations reflect credit on the publishers.

Les Astéréognosies: Pathologie du Toucher. Par J. P. L. DELAY. Paris: Masson et Cie. 1935. Pp. 524. Price 65 Fr.

Although primarily devoted to a study of astereognosis this monograph is, in fact, a review of our present conception of the physiology of sensation, for almost all its components may be concerned in the faculty of recognizing the form of objects, or in identifying them, by touch or handling.

The author starts with an analysis of the conditions under which astereognosis occurs, discusses the pathogenesis of each and its significance in topographical diagnosis. When unaccompanied by loss of any of the elementary forms of sensation the disturbance is at the intellectual level and is essentially an agnosia, but in the more common types there is always some sensory defect, either in the spatial functions, which he terms morphognosis, or in the recognition of specific qualities of the test objects, which he speaks of as hylognosis. He follows closely Sir Henry Head's observations and conclusions and differs from them in minor details only. He recognizes the important part in the production of astereognosis which may be played by the lability of threshold and perseverations of responses which were first shown by Head and his collaborators to characterize cortical lesions, and which were later described by German authors as "Funktionswandel." The significance in stereognosis of the "Gestalt Theorie," that the recognition of the whole precedes that of its parts, and of the ordinary view, that a knowledge of the whole is arrived at by the intellectual synthesis of the separate impressions excited by it, are discussed, and the nature of "tactile agnosia" is adequately dealt with.

The monograph suffers from the fact that the greater number of the observations used by the author in his arguments were collected from the literature, for in the delicate task of investigating sensory abnormalities much depends on the personal equation, but it can be strongly recommended as an excellent and readable presentation of our present views on the organization of sensation.

A Preface to Nervous Disease. By STANLEY COBB. London: Baillière, Tindall & Cox. 1936. Pp: 173. Price 13s. 6d.

For such a book as this many teachers of neurology have for long wished. In it the author has crystalized and presented lucidly the more essential facts of to-day's knowledge of the structure and functions of the nervous system from the psychological as well as the neurological aspect, for one chapter deals with "Consciousness and the Mind-body Problem," and in another the essential nature of the psychoses is discussed; it will be therefore useful as a fundamental introduction to the physiological study of mental disease. It is not a book for the junior student; for him the subject matter is treated too concisely and in places perhaps in too much detail, but it will be a safe guide and corrective to those who have already studied the rudiments of neurology and psychiatry. In this respect the earlier chapters, especially those on the organization of the central nervous system, on motor integration and locomotion, and on the cerebral circulation, are extremely valuable and instructive. The chapters on the pathology of the nervous system attain the same high level, though after having read the earlier sections many will regret they occupy so many of the author's pages.

Physiopathologie du Système Nerveux. Par P. COSSA. Paris: Masson et Cie. 1936. Pp. 690. Price 75 Fr.

The sub-title of this interesting book, " Mecanisme au Diagnostic " indicates its scope and aim. The author describes shortly and illustrates by simple diagrams the anatomical basis of each function, discusses its physiology and then deals briefly with the disturbances which constitute the symptoms of its disease, but the latter is a less essential feature of his work. The anatomy and physiology are, within the imposed limits, sound, though naturally such simplification as the author attempts must in places expose him to criticism. He has, however, succeeded in producing an excellent and extremely useful book for the student of neurology. An index adds to its value.

Otologische Diagnostik der Hirntumoren. von H. BRUNNER. Berlin: Urban und Schwarzenberg. 1936. S. 285. Price RM. 8.

This study by a well-known Viennese otologist of the disorders of hearing and of labyrinthine functions in intracranial tumours is an important contribution to their symptomatology, though the author recognizes that, except in tumours of the posterior fossa, these disorders contribute little to diagnosis. A special feature of his work was the anatomical examination of the inner ear as well as of the brain in all cases which came to autopsy. The pathological findings are carefully described and liberally illustrated; they include hyperæmia, hæmorrhages and exudates in the labyrinth and cochlea in acute or varying intracranial pressure, and degenerative changes in the nerves and ganglia, especially in the vestibular, in association with tumours of the 8th nerve.

The chapters on deafness in mesencephalic tumours and on disturbances of hearing in cerebellar growths, and their differential diagnosis, are of particular interest, as also is the question of labyrinthine over-excitability in both infra- and supra-tentorial tumours.

Synthèse des Voies de Conduction des Centres Nerveux. Par E. LEBLANC. Paris: Félix Alcan. 1935. Pp. 235. Price 50 Fr.

To junior neurologists and students who lack the opportunity or interest to obtain an intimate knowledge of the anatomy of the central nervous system this book will be useful. The anatomical connections and relations of separate systems are described concisely in short chapters and paragraphs, and copiously illustrated by simple diagrams which are often crude, but as accurate on the whole as diagrams can be expected to be. There are also short references to the disturbances of function which result from local lesions involving different conducting paths. Such a patchy acquaintance with anatomy as can be thus obtained is obviously unsatisfactory, but of its type this book is good.

Gefässmissbildungen und Gefässgeschwülste des Gehirns. von H. BERGSTRAND, H. OLIVECRONA und W. TÖNNIS. Leipzig: G. Thieme. 1936. S. 181. Price RM. 24.

This noteworthy contribution to vascular abnormalities and tumours in the central nervous system is introduced by a long chapter on their pathology by Bergstrand. He adopts Virchow's original classification of angiomata into cavernous and racemose types and his subdivision of the latter into different sub-groups, in fact he can add to it only the Lindau tumours and the rare condition described by Roussy and Oberling as angioglioma. The pathological anatomy and the origin of all these conditions are clearly described and excellently illustrated. The clinical and surgical sections have been written by Olivecrona and Tönnis; the former deals with the Sturge-Weber syndrome and angio-reticulomata or Lindau's disease, the latter with arteriovenous aneurisms and venous racemose angiomata. The clinical features, differential diagnosis and treatment of each form are carefully and fully considered. The production of the book, and especially of the illustrations, deserves much praise.

Dystrophia Musculorum Progressiva: Eine erblichkeitsmedizinische und klinische Studie. von B. SJÖVALL. Lund: Berlingska Boktryckeriet. 1936. S. 240.

This study of the muscular dystrophies, chiefly from the point of view of their inheritance, was made on a large personally observed material in Sweden. The author's conclusion is that there is probably more than one type of heredity. The clinical features, related abnormalities, and the course and prognosis of the disease are also discussed.

Investigation on Epilepsy and Water Metabolism. By H. P. STUBBE TEGLBJAERG. Copenhagen: Levin and Munksgaard. 1936. Pp. 247.

The chief conclusions drawn from this carefully controlled and well-documented study are, that the water balance is more unstable in epileptics than in normal persons, usually in the direction of excessive retention, though seizures are not associated with any contemporary change in it; that a dry diet régime is helpful in the treatment of many cases of epilepsy; that the relation of epilepsy and water metabolism probably depends on a focal susceptibility of nervous cells, and that "hyperhydration" is an effective method of exciting, for the purpose of observation, seizures in those liable to them.

Les Spasmes de la Face et Leur Traitement. Par Th. ALAJOUANINE et R. THUREL. Paris: Masson et Cie. 1936. Pp. 88. Price 12 Fr.

This small monograph deals with various types of involuntary movements of the face, including both the tics and those of peripheral and central organic origin. It will prove useful to the practitioner in his diagnosis and treatment.

La Radiothérapie des Syndromes Organo-Végétatifs (*Sympathicotonies, Vagotonies, Amphotonies*). Par L. DELHERM et H. BEAU. Paris: Masson et Cie. 1935. P. 158. Price 22 Fr.

After a short review of the action of X-rays on tissues, the authors concentrate on the value of treatment by this means of affections resulting from disorders of the autonomic system. In their review they include many morbid conditions in which this pathogenic rôle is not generally accepted, but their methods and the results they claim to have obtained are instructive. The literature on the subject is critically analysed. The book should prove useful to those engaged in radiotherapy.

Nouveau Traité de Psychologie. Tome V. Par B. BOURDON et H. DELACROIX. Paris: Félix Alcan. 1936. Pp. 404. Price 75 Fr.

This fifth volume of Prof. Dumas's admirably planned series deals with the systematized functions of intellectual life. The opening article, on perception, is by Prof. B. Bourdon, who follows orthodox lines, subdividing his material according to its sensory quality and paying adequate attention to the work of the "Gestalt" school: he does not, however, make use of the rich material available in clinical neurology and psychiatry, as may be seen in his section on visual, tactile and auditory space perception. The other three articles are all from the expert hand of Henri Delacroix. In the first he examines the intellectual operations concerned in thought, judgment, understanding, and language—topics on which, as ever, he writes easily and lucidly. His second article is devoted to belief and reason; in the earlier part he discusses the psychological factors in faith and certainty, and in the latter part, the nature and function of intelligence. Many important problems, such as animal intelligence, so-called prelogical mentality and magic, are here critically elucidated. In his last article he considers memories, as they may be variously studied from the point of view of consciousness of time, and the functions of memory and intelligence: there is a final brief excursus on dreams and reveries. So vast is the literature on the subjects treated in this volume that the reader is grateful for a continuously readable text, neither loaded nor interrupted by references to the discordant authorities; the bibliographies, however, are unduly select.

Theory and Practice of Psychiatry. By WILLIAM S. SADLER. London: Henry Kimpton. 1936. Pp. 1231. Price 42s.

This is the biggest single textbook of psychiatry in English, if not in any language. It is, however, much bigger than its contents require. Psychiatry is notoriously a subject which it is difficult to present or discuss concisely, but such extreme discursiveness as may be found in this book is certainly not inherent in the subject. The range of topics goes beyond what may be called medical, and seems to support the view that psychiatrists who are mainly occupied with psychotherapy tend to be more interested in a philosophy of life than in strict observation and disciplined thinking.

Vom Sinn der Sinne. von ERWIN STRAUS. Berlin: Springer. 1935. S. 314.

In this difficult but instructive study the problem of sensation is analysed with remarkable freshness and profundity. The enormous influence of Descartes upon psychology is the subject of an erudite opening section, and the bearing of this upon Pavlov's theories is critically considered in a series of chapters dealing with spatial localization, succession in time, and the meaning of the "signal" as it is understood in the doctrine of conditioned reflexes. The author presents his own views of sensation, which are subtle and complex. He prefers to regard sensation as separate from perception, and to distinguish between the dynamic process of sensation and the corresponding physical happening. In further developing his conceptions, which are of a philosophical tenor, he brings in his theory of movement and of the nature of time and space; incidentally he refutes epiphenomenalism, of which he considers Köhler and other Gestalt psychologists to be modern proponents. His conclusions do not lend themselves to summary presentation.

Die defektschizophrenen Krankheitsbilder. von K. LEONHARD. Leipzig: Georg Thieme. 1936. S. 134. Price RM. 8.70.

The author's object was to divide up schizophrenia according to the clinical state reached after patients had suffered from the chronic form of the illness for ten years or more. By a somewhat arbitrary method he apportions his cases into no less than fourteen groups, which correspond closely to those delimited in acute cases by Professor Kleist, with whom he has been working. It cannot be said that his method of classification is easy to grasp or to apply. The atypical fifth of his cases had a heavy hereditary taint and were dependent on exogenous factors: since, however, they were prone to follow a periodic course, it seems likely that some of the genetic factors at work were those concerned in manic-depressive psychosis.

The Visual Perception of Space. By A. A. H. EL KOUSSY. London: Cambridge University Press. 1935. Pp. 89. Price 8s. 6d.

The mathematical devices by which Professor Spearman has enriched psychology, are here applied to the field of spatial perception. It is concluded that some spatial tests involve a group factor, called "K," which is closely concerned with the ability to obtain, manipulate and utilize visual spatial imagery. The emphasis put by Dr. Koussy upon the visual element in spatial perception would seem, from clinical data, to express an unduly simplified view of the relations. The author first surveys the range and theories of spatial tests and the correlational studies of the problem; he then describes his tests and his statistical treatment of the data, concluding his thesis with an explanation of the "K" factor based mainly on introspective reports.

Sex and Personality. By L. W. TERMAN and C. C. MILES. London: McGraw-Hill. 1936. Pp. 600. Price 25s.

An attempt has been made by Professor Terman and his co-workers during the last eleven years to work out tests which would quantify differences in masculinity and femininity, much as differences in intelligence were made accessible to measurement by Binet and his successors, among whom Professor Terman has been so prominent. The vagueness of the whole subject has made the authors reluctant to see in the painstaking experiments here reported anything more than a preliminary study. Their statistical method of determining what tests were significant is, as might be expected, unexceptionable, and their cautious statement of results gained on a large and varied material, including homosexuals and delinquents, provides a valuable basis for further scientific work. The book is fully documented and suggests many fields, including psychiatry, to which the method might be further applied.

Methodik der medizinischen Erbforschung: unter besonderer Berücksichtigung der Psychiatrie. von B. SCHULZ. Leipzig: Thieme. 1936. S. 189. RM. 10.50.

The lack of an authoritative work on methods of investigating the heredity of mental disorder is made good by this monograph. Although much of it is applicable to medicine generally, the author's experience has been gained in the specially difficult field of psychiatry. After an introductory review of the problems Dr. Schulz describes in detail the methods of ascertainment and evaluation, paying regard also to supplementary methods, such as investigation of twins. The weakest feature of his book is the statistical part in which he does not do justice to modern developments in the treatment of small samples. His exposition is, however, adequate for most purposes and should be indispensable to investigators who have not received a training in both genetics and psychiatry.

Tentatives Opératoires dans le Traitement de Certaines Psychoses. Par E. MONIZ. Paris: Masson et Cie. 1936. P. 248. Price 40 Fr.

The author started with the assumption that certain mental disturbances in the insane result from faulty anatomical associations, chiefly in the frontal lobes, and he therefore hoped to relieve the symptoms by interrupting these anatomical paths. His operation consists in injection of alcohol into, or excision of part of, the white matter of the frontal lobes. He claims that one-third of the patients operated on were cured and another third greatly relieved. Chapters on the functions of the frontal lobes stand on a par with the rest of the book.

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A JOURNAL OF NEUROLOGY,
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VOL. LIX, 1936.

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